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8 A2

(54) Title: COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF LUNG CANCER

(57) Abstract: Compositions and methods for the therapy and diagnosis of cancer, such as lung cancer, are disclosed. Compositions may comprise one or more lung tumor proteins, immunogenic portions thereof, or polynucleotides that encode such portions. Alternatively, a therapeutic composition may comprise an antigen presenting cell that expresses a lung tumor protein, or a T cell that is specific for cells expressing such a protein. Such compositions may be used, for example, for the prevention and treatment of diseases such as lung cancer. Diagnostic methods based on detecting a lung tumor protein, or mRNA encoding such a protein, in a sample are also provided.

COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF LUNG CANCER

TECHNICAL FIELD OF THE INVENTION

The present invention relates generally to therapy and diagnosis of cancer, such as lung cancer. The invention is more specifically related to polypeptides comprising at least a portion of a lung tumor protein, and to polynucleotides encoding such polypeptides. Such polypeptides and polynucleotides may be used in compositions for prevention and treatment of lung cancer, and for the diagnosis and monitoring of such cancers.

10 BACKGROUND OF THE INVENTION

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Cancer is a significant health problem throughout the world. Although advances have been made in detection and therapy of cancer, no vaccine or other universally successful method for prevention or treatment is currently available. Current therapies, which are generally based on a combination of chemotherapy or surgery and radiation, continue to prove inadequate in many patients.

Lung cancer is the primary cause of cancer death among both men and women in the U.S., with an estimated 172,000 new cases being reported in 1994. The five-year survival rate among all lung cancer patients, regardless of the stage of disease at diagnosis, is only 13%. This contrasts with a five-year survival rate of 46% among cases detected while the disease is still localized. However, only 16% of lung cancers are discovered before the disease has spread.

Early detection is difficult since clinical symptoms are often not seen until the disease has reached an advanced stage. Currently, diagnosis is aided by the use of chest x-rays, analysis of the type of cells contained in sputum and fiberoptic examination of the bronchial passages. Treatment regimens are determined by the type and stage of the cancer, and include surgery, radiation therapy and/or chemotherapy.

In spite of considerable research into therapies for this and other cancers, lung cancer remains difficult to diagnose and treat effectively. Accordingly, there is a

need in the art for improved methods for detecting and treating such cancers. The present invention fulfills these needs and further provides other related advantages.

SUMMARY OF THE INVENTION

Briefly stated, the present invention provides compositions and methods for the diagnosis and therapy of cancer, such as lung cancer. In one aspect, the present 5 invention provides polypeptides comprising at least a portion of a lung tumor protein, or a variant thereof. Certain portions and other variants are immunogenic, such that the ability of the variant to react with antigen-specific antisera is not substantially diminished. Within certain embodiments, the polypeptide comprises a sequence that is encoded by a polynucleotide sequence selected from the group consisting of: (a) 10 sequences recited in SEO ID NO: 1, 11-13, 15, 20, 23-27, 29, 30, 33, 34, 39, 41, 43-46, 51, 52, 57, 58, 60, 62, 65-67, 69-71, 74, 76, 79, 80, 84, 86, 89-92, 95, 97, 98, 101, 110, 111, 113-119, 121-128, 130-134, 136, 138, 139, 141, 143, 146-151, 153, 154, 157-160, 162-164, 167-178, 180, 181, 183, 186-190, 192, 193, 195-220, 224, 226-231, 234, 236, 237, 240, 241, 244-246, 248, 254, 255, 261, 262, 266, 270, 275, 280, 282, 283, 288, 15 289, 290, 292, 295, 301, 303, 304, 309, 311, 341-782, 784, 785, 790, 792, 794, 796, 800-804, 807, 808 and 810-826; (b) variants of a sequence recited in SEQ ID NO: 1, 11-13, 15, 20, 23-27, 29, 30, 33, 34, 39, 41, 43-46, 51, 52, 57, 58, 60, 62, 65-67, 69-71, 74, 76, 79, 80, 84, 86, 89-92, 95, 97, 98, 101, 110, 111, 113-119, 121-128, 130-134, 20 136, 138, 139, 141, 143, 146-151, 153, 154, 157-160, 162-164, 167-178, 180, 181, 183, 186-190, 192, 193, 195-220, 224, 226-231, 234, 236, 237, 240, 241, 244-246, 248, 254, 255, 261, 262, 266, 270, 275, 280, 282, 283, 288, 289, 290, 292, 295, 301, 303, 304, 309, 311, 341-782, 784, 785, 790, 792, 794, 796, 800-804, 807, 808 and 810-826; and (c) complements of a sequence of (a) or (b). In specific embodiments, the polypeptides of the present invention comprise at least a portion of a tumor protein that includes an 25 amino acid sequence selected from the group consisting of sequences recited in SEQ ID NO: 786, 787, 791, 793, 795, 797-799, 806, 809 and 827, and variants thereof.

The present invention further provides polynucleotides that encode a polypeptide as described above, or a portion thereof (such as a portion encoding at least

15 amino acid residues of a lung tumor protein), expression vectors comprising such polynucleotides and host cells transformed or transfected with such expression vectors.

Within other aspects, the present invention provides pharmaceutical compositions comprising a polypeptide or polynucleotide as described above and a physiologically acceptable carrier.

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Within a related aspect of the present invention, vaccines, or immunogenic compositions, for prophylactic or therapeutic use are provided. Such vaccines comprise a polypeptide or polynucleotide as described above and an immunostimulant.

The present invention further provides pharmaceutical compositions that comprise: (a) an antibody or antigen-binding fragment thereof that specifically binds to a lung tumor protein; and (b) a physiologically acceptable carrier.

Within further aspects, the present invention provides pharmaceutical compositions comprising: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) a pharmaceutically acceptable carrier or excipient. Antigen presenting cells include dendritic cells, macrophages, monocytes, fibroblasts and B cells.

Within related aspects, vaccines, or immunogenic compositions, are provided that comprise: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) an immunostimulant.

The present invention further provides, in other aspects, fusion proteins that comprise at least one polypeptide as described above, as well as polynucleotides encoding such fusion proteins.

Within related aspects, pharmaceutical compositions comprising a fusion protein, or a polynucleotide encoding a fusion protein, in combination with a physiologically acceptable carrier are provided.

Vaccines, or immunogenic compositions, are further provided, within other aspects, that comprise a fusion protein, or a polynucleotide encoding a fusion protein, in combination with an immunostimulant.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a

patient a pharmaceutical composition or immunogenic composition as recited above. The patient may be afflicted with lung cancer, in which case the methods provide treatment for the disease, or patient considered at risk for such a disease may be treated prophylactically.

The present invention further provides, within other aspects, methods for removing tumor cells from a biological sample, comprising contacting a biological sample with T cells that specifically react with a lung tumor protein, wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the protein from the sample.

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Within related aspects, methods are provided for inhibiting the development of a cancer in a patient, comprising administering to a patient a biological sample treated as described above.

Methods are further provided, within other aspects, for stimulating and/or expanding T cells specific for a lung tumor protein, comprising contacting T cells with one or more of: (i) a polypeptide as described above; (ii) a polynucleotide encoding such a polypeptide; and/or (iii) an antigen presenting cell that expresses such a polypeptide; under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells. Isolated T cell populations comprising T cells prepared as described above are also provided.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a T cell population as described above.

The present invention further provides methods for inhibiting the development of a cancer in a patient, comprising the steps of: (a) incubating CD4⁺ and/or CD8⁺ T cells isolated from a patient with one or more of: (i) a polypeptide comprising at least an immunogenic portion of a lung tumor protein; (ii) a polynucleotide encoding such a polypeptide; and (iii) an antigen-presenting cell that expressed such a polypeptide; and (b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of a cancer in the patient. Proliferated cells may, but need not, be cloned prior to administration to the patient.

Within further aspects, the present invention provides methods for determining the presence or absence of a cancer in a patient, comprising: (a) contacting a biological sample obtained from a patient with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; and (c) comparing the amount of polypeptide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within preferred embodiments, the binding agent is an antibody, more preferably a monoclonal antibody. The cancer may be lung cancer.

The present invention also provides, within other aspects, methods for monitoring the progression of a cancer in a patient. Such methods comprise the steps of: (a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polypeptide detected in step (c) with the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

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The present invention further provides, within other aspects, methods for determining the presence or absence of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a lung tumor protein; (b) detecting in the sample a level of a polynucleotide, preferably mRNA, that hybridizes to the oligonucleotide; and (c) comparing the level of polynucleotide that hybridizes to the oligonucleotide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within certain embodiments, the amount of mRNA is detected via polymerase chain reaction using, for example, at least one oligonucleotide primer that hybridizes to a polynucleotide encoding a polypeptide as recited above, or a complement of such a polynucleotide. Within other embodiments, the amount of mRNA is detected using a hybridization technique, employing an oligonucleotide probe that hybridizes to a polynucleotide that encodes a polypeptide as recited above, or a complement of such a polynucleotide that encodes a polypeptide as recited above, or a complement of such a polynucleotide.

In related aspects, methods are provided for monitoring the progression of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a lung tumor protein; (b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polynucleotide detected in step (c) with the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

Within further aspects, the present invention provides antibodies, such as monoclonal antibodies, that bind to a polypeptide as described above, as well as diagnostic kits comprising such antibodies. Diagnostic kits comprising one or more oligonucleotide probes or primers as described above are also provided.

These and other aspects of the present invention will become apparent upon reference to the following detailed description and attached drawings. All references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

SEQUENCE IDENTIFIERS

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SEQ ID NO: 1 is the determined cDNA sequence for clone #19038, also referred to as L845P.

SEQ ID NO: 2 is the determined cDNA sequence for clone #19036.

SEQ ID NO: 3 is the determined cDNA sequence for clone #19034.

SEQ ID NO: 4 is the determined cDNA sequence for clone #19033.

SEQ ID NO: 5 is the determined cDNA sequence for clone #19032.

SEQ ID NO: 6 is the determined cDNA sequence for clone #19030, also

25 referred to as L559S.

SEQ ID NO: 7 is the determined cDNA sequence for clone #19029.

SEQ ID NO: 8 is the determined cDNA sequence for clone #19025.

SEQ ID NO: 9 is the determined cDNA sequence for clone #19023.

SEQ ID NO: 10 is the determined cDNA sequence for clone #18929.

30 SEQ ID NO: 11 is the determined cDNA sequence for clone #19010.

SEQ ID NO: 12 is the determined cDNA sequence for clone #19009. SEQ ID NO: 13 is the determined cDNA sequence for clones #19005, 19007, 19016 and 19017. SEQ ID NO: 14 is the determined cDNA sequence for clone #19004. 5 SEQ ID NO: 15 is the determined cDNA sequence for clones #19002 and 18965. SEQ ID NO: 16 is the determined cDNA sequence for clone #18998. SEQ ID NO: 17 is the determined cDNA sequence for clone #18997. SEO ID NO: 18 is the determined cDNA sequence for clone #18996. SEQ ID NO: 19 is the determined cDNA sequence for clone #18995. 10 SEQ ID NO: 20 is the determined cDNA sequence for clone #18994, also known as L846P. SEO ID NO: 21 is the determined cDNA sequence for clone #18992. SEO ID NO: 22 is the determined cDNA sequence for clone #18991. SEO ID NO: 23 is the determined cDNA sequence for clone #18990, 15 also referred to as clone #20111. SEQ ID NO: 24 is the determined cDNA sequence for clone #18987. SEQ ID NO: 25 is the determined cDNA sequence for clone #18985, also referred as L839P. SEO ID NO: 26 is the determined cDNA sequence for clone #18984, 20 also referred to as L847P. SEQ ID NO: 27 is the determined cDNA sequence for clone #18983. SEQ ID NO: 28 is the determined cDNA sequence for clones #18976 and 18980. SEQ ID NO: 29 is the determined cDNA sequence for clone #18975. 25 SEQ ID NO: 30 is the determined cDNA sequence for clone #18974. SEQ ID NO: 31 is the determined cDNA sequence for clone #18973. SEQ ID NO: 32 is the determined cDNA sequence for clone #18972. SEQ ID NO: 33 is the determined cDNA sequence for clone #18971, also referred to as L801P. 30 SEQ ID NO: 34 is the determined cDNA sequence for clone #18970.

SEQ ID NO: 35 is the determined cDNA sequence for clone #18966.

SEQ ID NO: 36 is the determined cDNA sequence for clones #18964, 18968 and 19039.

SEQ ID NO: 37 is the determined cDNA sequence for clone #18960.

SEQ ID NO: 38 is the determined cDNA sequence for clone #18959.

SEQ ID NO: 39 is the determined cDNA sequence for clones #18958 and 18982.

SEQ ID NO: 40 is the determined cDNA sequence for clones #18956 and 19015.

SEQ ID NO: 41 is the determined cDNA sequence for clone #18954, also referred to L848P.

SEQ ID NO: 42 is the determined cDNA sequence for clone #18951.

SEQ ID NO: 43 is the determined cDNA sequence for clone #18950.

SEQ ID NO: 44 is the determined cDNA sequence for clones #18949 and 19024, also referred to as L844P.

SEQ ID NO: 45 is the determined cDNA sequence for clone #18948.

SEQ ID NO: 46 is the determined cDNA sequence for clone #18947, also referred to as L840P.

SEQ ID NO: 47 is the determined cDNA sequence for clones #18946, 20 18953, 18969 and 19027.

SEQ ID NO: 48 is the determined cDNA sequence for clone #18942.

SEQ ID NO: 49 is the determined cDNA sequence for clone #18940, 18962, 18963, 19006, 19008, 19000, and 19031.

SEQ ID NO: 50 is the determined cDNA sequence for clone #18939.

SEQ ID NO: 51 is the determined cDNA sequence for clones #18938 and 18952.

SEQ ID NO: 52 is the determined cDNA sequence for clone #18938.

SEQ ID NO: 53 is the determined cDNA sequence for clone #18937.

SEQ ID NO: 54 is the determined cDNA sequence for clones #18934,

30 18935, 18993 and 19022, also referred to as L548S.

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SEQ ID NO: 55 is the determined cDNA sequence for clone #18932.

SEQ ID NO: 56 is the determined cDNA sequence for clones #18931 and 18936. SEQ ID NO: 57 is the determined cDNA sequence for clone #18930. SEQ ID NO: 58 is the determined cDNA sequence for clone #19014, 5 also referred to as L773P. SEQ ID NO: 59 is the determined cDNA sequence for clone #19127. SEO ID NO: 60 is the determined cDNA sequence for clones #19057 and 19064. SEQ ID NO: 61 is the determined cDNA sequence for clone #19122. 10 SEQ ID NO: 62 is the determined cDNA sequence for clones #19120 and 18121. SEQ ID NO: 63 is the determined cDNA sequence for clone #19118. SEQ ID NO: 64 is the determined cDNA sequence for clone #19117. SEQ ID NO: 65 is the determined cDNA sequence for clone #19116. SEO ID NO: 66 is the determined cDNA sequence for clone #19114. 15 SEQ ID NO: 67 is the determined cDNA sequence for clone #19112, also known as L561S. SEQ ID NO: 68 is the determined cDNA sequence for clone #19110. SEO ID NO: 69 is the determined cDNA sequence for clone #19107, 20 also referred to as L552S. SEO ID NO: 70 is the determined cDNA sequence for clone #19106, also referred to as L547S. SEO ID NO: 71 is the determined cDNA sequence for clones #19105 and 19111. SEO ID NO: 72 is the determined cDNA sequence for clone #19099. 25 SEQ ID NO: 73 is the determined cDNA sequence for clones #19095, 19104 and 19125, also referred to as L549S. SEQ ID NO: 74 is the determined cDNA sequence for clone #19094. SEQ ID NO: 75 is the determined cDNA sequence for clones #19089 30 and 19101. SEO ID NO: 76 is the determined cDNA sequence for clone #19088.

SEQ ID NO: 77 is the determined cDNA sequence for clones #19087, 19092, 19096, 19100 and 19119.

SEQ ID NO: 78 is the determined cDNA sequence for clone #19086.

SEQ ID NO: 79 is the determined cDNA sequence for clone #19085,

5 also referred to as L550S.

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SEQ ID NO: 80 is the determined cDNA sequence for clone #19084, also referred to as clone #19079.

SEQ ID NO: 81 is the determined cDNA sequence for clone #19082.

SEQ ID NO: 82 is the determined cDNA sequence for clone #19080.

SEQ ID NO: 83 is the determined cDNA sequence for clone #19077.

SEQ ID NO: 84 is the determined cDNA sequence for clone #19076, also referred to as L551S.

SEQ ID NO: 85 is the determined cDNA sequence for clone #19074, also referred to as clone #20102.

SEQ ID NO: 86 is the determined cDNA sequence for clone #19073, also referred to as L560S.

SEQ ID NO: 87 is the determined cDNA sequence for clones #19072 and 19115.

SEQ ID NO: 88 is the determined cDNA sequence for clone #19071.

SEQ ID NO: 89 is the determined cDNA sequence for clone #19070.

SEQ ID NO: 90 is the determined cDNA sequence for clone #19069.

SEQ ID NO: 91 is the determined cDNA sequence for clone #19068, also referred to L563S.

SEQ ID NO: 92 is the determined cDNA sequence for clone #19066.

SEQ ID NO: 93 is the determined cDNA sequence for clone #19065.

SEQ ID NO: 94 is the determined cDNA sequence for clone #19063.

SEQ ID NO: 95 is the determined cDNA sequence for clones #19061, 19081, 19108 and 19109.

SEQ ID NO: 96 is the determined cDNA sequence for clones #19060, 30 19067 and 19083, also referred to as L548S.

SEQ ID NO: 97 is the determined cDNA sequence for clones #19059 and 19062. SEO ID NO: 98 is the determined cDNA sequence for clone #19058. SEQ ID NO: 99 is the determined cDNA sequence for clone #19124. 5 SEQ ID NO: 100 is the determined cDNA sequence for clone #18929. SEQ ID NO: 101 is the determined cDNA sequence for clone #18422. SEQ ID NO: 102 is the determined cDNA sequence for clone #18425. SEQ ID NO: 103 is the determined cDNA sequence for clone #18431. SEQ ID NO: 104 is the determined cDNA sequence for clone #18433. SEO ID NO: 105 is the determined cDNA sequence for clone #18444. 10 SEQ ID NO: 106 is the determined cDNA sequence for clone #18449. SEO ID NO: 107 is the determined cDNA sequence for clone #18451. SEQ ID NO: 108 is the determined cDNA sequence for clone #18452. SEO ID NO: 109 is the determined cDNA sequence for clone #18455. SEQ ID NO: 110 is the determined cDNA sequence for clone #18457. 15 SEO ID NO: 111 is the determined cDNA sequence for clone #18466. SEO ID NO: 112 is the determined cDNA sequence for clone #18468. SEQ ID NO: 113 is the determined cDNA sequence for clone #18471. SEQ ID NO: 114 is the determined cDNA sequence for clone #18475. SEQ ID NO: 115 is the determined cDNA sequence for clone #18476. 20 SEO ID NO: 116 is the determined cDNA sequence for clone #18477. SEO ID NO: 117 is the determined cDNA sequence for clone #20631. SEQ ID NO: 118 is the determined cDNA sequence for clone #20634. SEO ID NO: 119 is the determined cDNA sequence for clone #20635. SEO ID NO: 120 is the determined cDNA sequence for clone #20637. 25 SEQ ID NO: 121 is the determined cDNA sequence for clone #20638. SEQ ID NO: 122 is the determined cDNA sequence for clone #20643. SEQ ID NO: 123 is the determined cDNA sequence for clone #20652.

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SEQ ID NO: 124 is the determined cDNA sequence for clone #20653.

SEQ ID NO: 125 is the determined cDNA sequence for clone #20657.

SEQ ID NO: 126 is the determined cDNA sequence for clone #20658.

SEQ ID NO: 127 is the determined cDNA sequence for clone #20660. SEQ ID NO: 128 is the determined cDNA sequence for clone #20661. SEQ ID NO: 129 is the determined cDNA sequence for clone #20663. SEQ ID NO: 130 is the determined cDNA sequence for clone #20665. 5 SEQ ID NO: 131 is the determined cDNA sequence for clone #20670. SEQ ID NO: 132 is the determined cDNA sequence for clone #20671. SEQ ID NO: 133 is the determined cDNA sequence for clone #20672. SEQ ID NO: 134 is the determined cDNA sequence for clone #20675. SEQ ID NO: 135 is the determined cDNA sequence for clone #20679. 10 SEQ ID NO: 136 is the determined cDNA sequence for clone #20681. SEQ ID NO: 137 is the determined cDNA sequence for clone #20682. SEQ ID NO: 138 is the determined cDNA sequence for clone #20684. SEQ ID NO: 139 is the determined cDNA sequence for clone #20685. SEQ ID NO: 140 is the determined cDNA sequence for clone #20689. 15 SEQ ID NO: 141 is the determined cDNA sequence for clone #20699. SEQ ID NO: 142 is the determined cDNA sequence for clone #20701. SEQ ID NO: 143 is the determined cDNA sequence for clone #20702. SEQ ID NO: 144 is the determined cDNA sequence for clone #20708. SEQ ID NO: 145 is the determined cDNA sequence for clone #20715. 20 SEQ ID NO: 146 is the determined cDNA sequence for clone #20716. SEQ ID NO: 147 is the determined cDNA sequence for clone #20719. SEQ ID NO: 148 is the determined cDNA sequence for clone #19129. SEQ ID NO: 149 is the determined cDNA sequence for clone #19131.1. SEQ ID NO: 150 is the determined cDNA sequence for clone #19132.2. 25 SEQ ID NO: 151 is the determined cDNA sequence for clone #19133. SEQ ID NO: 152 is the determined cDNA sequence for clone #19134.2. SEQ ID NO: 153 is the determined cDNA sequence for clone #19135.2. SEQ ID NO: 154 is the determined cDNA sequence for clone #19137. SEQ ID NO: 155 is a first determined cDNA sequence for clone 30 #19138.1.

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		SEQ ID NO: 156 is a second determined cDNA sequence for clone
	#19138.2.	
		SEQ ID NO: 157 is the determined cDNA sequence for clone #19139.
		SEQ ID NO: 158 is a first determined cDNA sequence for clone
5	#19140.1.	
		SEQ ID NO: 159 is a second determined cDNA sequence for clone
	#19140.2.	•
		SEQ ID NO: 160 is the determined cDNA sequence for clone #19141.
		SEQ ID NO: 161 is the determined cDNA sequence for clone #19143.
10		SEQ ID NO: 162 is the determined cDNA sequence for clone #19144.
		SEQ ID NO: 163 is a first determined cDNA sequence for clone
	#19145.1.	
		SEQ ID NO: 164 is a second determined cDNA sequence for clone
	#19145.2.	•
15		SEQ ID NO: 165 is the determined cDNA sequence for clone #19146.
		SEQ ID NO: 166 is the determined cDNA sequence for clone #19149.1.
		SEQ ID NO: 167 is the determined cDNA sequence for clone #19152.
		SEQ ID NO: 168 is a first determined cDNA sequence for clone
	#19153.1.	
20		SEQ ID NO: 169 is a second determined cDNA sequence for clone
	#19153.2.	
	•	SEQ ID NO: 170 is the determined cDNA sequence for clone #19155.
		SEQ ID NO: 171 is the determined cDNA sequence for clone #19157.
		SEQ ID NO: 172 is the determined cDNA sequence for clone #19159.
25		SEQ ID NO: 173 is the determined cDNA sequence for clone #19160.
		SEQ ID NO: 174 is a first determined cDNA sequence for clone
	#19161.1.	
		SEQ ID NO: 175 is a second determined cDNA sequence for clone
	#19161.2.	
30		SEQ ID NO: 176 is the determined cDNA sequence for clone #19162.1.
		SEQ ID NO: 177 is the determined cDNA sequence for clone #19166.

SEQ ID NO: 178 is the determined cDNA sequence for clone #19169. SEQ ID NO: 179 is the determined cDNA sequence for clone #19171. SEQ ID NO: 180 is a first determined cDNA sequence for clone #19173.1. 5 SEQ ID NO: 181 is a second determined cDNA sequence for clone #19173.2. SEQ ID NO: 182 is the determined cDNA sequence for clone #19174.1. SEQ ID NO: 183 is the determined cDNA sequence for clone #19175. SEQ ID NO: 184 is the determined cDNA sequence for clone #19177. 10 SEQ ID NO: 185 is the determined cDNA sequence for clone #19178. SEQ ID NO: 186 is the determined cDNA sequence for clone #19179.1. SEQ ID NO: 187 is the determined cDNA sequence for clone #19179.2. SEQ ID NO: 188 is the determined cDNA sequence for clone #19180. SEQ ID NO: 189 is a first determined cDNA sequence for clone #19182.1. 15 SEO ID NO: 190 is a second determined cDNA sequence for clone #19182.2. SEO ID NO: 191 is the determined cDNA sequence for clone #19183.1. SEO ID NO: 192 is the determined cDNA sequence for clone #19185.1. 20 SEO ID NO: 193 is the determined cDNA sequence for clone #19187. SEQ ID NO: 194 is the determined cDNA sequence for clone #19188. SEQ ID NO: 195 is the determined cDNA sequence for clone #19190. SEQ ID NO: 196 is the determined cDNA sequence for clone #19191. SEQ ID NO: 197 is the determined cDNA sequence for clone #19192. 25 SEQ ID NO: 198 is the determined cDNA sequence for clone #19193. SEO ID NO: 199 is a first determined cDNA sequence for clone #19194.1. SEQ ID NO: 200 is a second determined cDNA sequence for clone #19194.2. 30 SEQ ID NO: 201 is the determined cDNA sequence for clone #19197.

		SEQ ID NO: 202 is a first determined cDNA sequence for clone
	#19200.1.	
		SEQ ID NO: 203 is a second determined cDNA sequence for clone
	#19200.2.	
5		SEQ ID NO: 204 is the determined cDNA sequence for clone #19202.
		SEQ ID NO: 205 is a first determined cDNA sequence for clone
	#19204.1.	
		SEQ ID NO: 206 is a second determined cDNA sequence for clone
	#19204.2.	
10		SEQ ID NO: 207 is the determined cDNA sequence for clone #19205.
		SEQ ID NO: 208 is a first determined cDNA sequence for clone
	#19206.1.	
		SEQ ID NO: 209 is a second determined cDNA sequence for clone
	#19206.2.	
15		SEQ ID NO: 210 is the determined cDNA sequence for clone #19207.
		SEQ ID NO: 211 is the determined cDNA sequence for clone #19208.
		SEQ ID NO: 212 is a first determined cDNA sequence for clone
	#19211.1.	
		SEQ ID NO: 213 is a second determined cDNA sequence for clone
20	#19211.2.	
		SEQ ID NO: 214 is a first determined cDNA sequence for clone
	#19214.1.	CDO ID NO 015 : 1 lateralised aDNA accounts for along
	//1001 A 0	SEQ ID NO: 215 is a second determined cDNA sequence for clone
25	#19214.2.	SEQ ID NO: 216 is the determined cDNA sequence for clone #19215.
25		SEQ ID NO: 217 is a first determined cDNA sequence for clone #19217.
	2.	SEQ ID NO. 217 is a first determined eDNA sequence for clone #17217.
	2.	SEQ ID NO: 218 is a second determined cDNA sequence for clone
	#19217.2.	DEQ 1D 110. 210 is a second determined edital sequence for cione
30	17 1 7 6 1 1 . 6 .	SEQ ID NO: 219 is a first determined cDNA sequence for clone
. U	#19218.1.	DEC 12 110. 217 to a mot determined optical sequence for element

SEQ ID NO: 220 is a second determined cDNA sequence for clone #19218.2. SEQ ID NO: 221 is a first determined cDNA sequence for clone #19220.1. 5 SEQ ID NO: 222 is a second determined cDNA sequence for clone #19220.2. SEQ ID NO: 223 is the determined cDNA sequence for clone #22015. SEQ ID NO: 224 is the determined cDNA sequence for clone #22017. SEQ ID NO: 225 is the determined cDNA sequence for clone #22019. 10 SEQ ID NO: 226 is the determined cDNA sequence for clone #22020. SEQ ID NO: 227 is the determined cDNA sequence for clone #22023. SEQ ID NO: 228 is the determined cDNA sequence for clone #22026. SEQ ID NO: 229 is the determined cDNA sequence for clone #22027. SEQ ID NO: 230 is the determined cDNA sequence for clone #22028. 15 SEQ ID NO: 231 is the determined cDNA sequence for clone #22032. SEQ ID NO: 232 is the determined cDNA sequence for clone #22037. SEQ ID NO: 233 is the determined cDNA sequence for clone #22045. SEQ ID NO: 234 is the determined cDNA sequence for clone #22048. SEQ ID NO: 235 is the determined cDNA sequence for clone #22050. 20 SEQ ID NO: 236 is the determined cDNA sequence for clone #22052. SEQ ID NO: 237 is the determined cDNA sequence for clone #22053. SEQ ID NO: 238 is the determined cDNA sequence for clone #22057. SEQ ID NO: 239 is the determined cDNA sequence for clone #22066. SEQ ID NO: 240 is the determined cDNA sequence for clone #22077. 25 SEQ ID NO: 241 is the determined cDNA sequence for clone #22085. SEQ ID NO: 242 is the determined cDNA sequence for clone #22105. SEQ ID NO: 243 is the determined cDNA sequence for clone #22108. SEQ ID NO: 244 is the determined cDNA sequence for clone #22109. SEQ ID NO: 245 is the determined cDNA sequence for clone #24842. 30 SEQ ID NO: 246 is the determined cDNA sequence for clone #24843. SEQ ID NO: 247 is the determined cDNA sequence for clone #24845.

	SEQ ID NO: 248 is the determined cDNA sequence for clone #24851.
	SEQ ID NO: 249 is the determined cDNA sequence for clone #24852.
	SEQ ID NO: 250 is the determined cDNA sequence for clone #24853.
	SEQ ID NO: 251 is the determined cDNA sequence for clone #24854.
5	SEQ ID NO: 252 is the determined cDNA sequence for clone #24855.
	SEQ ID NO: 253 is the determined cDNA sequence for clone #24860.
	SEQ ID NO: 254 is the determined cDNA sequence for clone #24864.
	SEQ ID NO: 255 is the determined cDNA sequence for clone #24866.
	SEQ ID NO: 256 is the determined cDNA sequence for clone #24867.
10	SEQ ID NO: 257 is the determined cDNA sequence for clone #24868.
	SEQ ID NO: 258 is the determined cDNA sequence for clone #24869.
	SEQ ID NO: 259 is the determined cDNA sequence for clone #24870.
	SEQ ID NO: 260 is the determined cDNA sequence for clone #24872.
	SEQ ID NO: 261 is the determined cDNA sequence for clone #24873.
15	SEQ ID NO: 262 is the determined cDNA sequence for clone #24875.
	SEQ ID NO: 263 is the determined cDNA sequence for clone #24882.
	SEQ ID NO: 264 is the determined cDNA sequence for clone #24885.
	SEQ ID NO: 265 is the determined cDNA sequence for clone #24886.
	SEQ ID NO: 266 is the determined cDNA sequence for clone #24887.
20	SEQ ID NO: 267 is the determined cDNA sequence for clone #24888.
	SEQ ID NO: 268 is the determined cDNA sequence for clone #24890.
	SEQ ID NO: 269 is the determined cDNA sequence for clone #24896.
	SEQ ID NO: 270 is the determined cDNA sequence for clone #24897.
	SEQ ID NO: 271 is the determined cDNA sequence for clone #24899.
25	SEQ ID NO: 272 is the determined cDNA sequence for clone #24901.
	SEQ ID NO: 273 is the determined cDNA sequence for clone #24902.
	SEQ ID NO: 274 is the determined cDNA sequence for clone #24906.
	SEQ ID NO: 275 is the determined cDNA sequence for clone #24912.
	SEQ ID NO: 276 is the determined cDNA sequence for clone #24913.
30	SEQ ID NO: 277 is the determined cDNA sequence for clone #24920.
	SEQ ID NO: 278 is the determined cDNA sequence for clone #24927.

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SEQ ID NO: 279 is the determined cDNA sequence for clone #24930. SEQ ID NO: 280 is the determined cDNA sequence for clone #26938. SEQ ID NO: 281 is the determined cDNA sequence for clone #26939. SEQ ID NO: 282 is the determined cDNA sequence for clone #26943. 5 SEQ ID NO: 283 is the determined cDNA sequence for clone #26948. SEQ ID NO: 284 is the determined cDNA sequence for clone #26951. SEQ ID NO: 285 is the determined cDNA sequence for clone #26955. SEQ ID NO: 286 is the determined cDNA sequence for clone #26956. SEQ ID NO: 287 is the determined cDNA sequence for clone #26959. 10 SEQ ID NO: 288 is the determined cDNA sequence for clone #26961. SEQ ID NO: 289 is the determined cDNA sequence for clone #26962. SEQ ID NO: 290 is the determined cDNA sequence for clone #26964. SEQ ID NO: 291 is the determined cDNA sequence for clone #26966. SEQ ID NO: 292 is the determined cDNA sequence for clone #26968. 15 SEQ ID NO: 293 is the determined cDNA sequence for clone #26972. SEQ ID NO: 294 is the determined cDNA sequence for clone #26973. SEQ ID NO: 295 is the determined cDNA sequence for clone #26974. SEQ ID NO: 296 is the determined cDNA sequence for clone #26976. SEQ ID NO: 297 is the determined cDNA sequence for clone #26977. 20 SEQ ID NO: 298 is the determined cDNA sequence for clone #26979. SEQ ID NO: 299 is the determined cDNA sequence for clone #26980. SEQ ID NO: 300 is the determined cDNA sequence for clone #26981. SEQ ID NO: 301 is the determined cDNA sequence for clone #26984. SEQ ID NO: 302 is the determined cDNA sequence for clone #26985. SEQ ID NO: 303 is the determined cDNA sequence for clone #26986. 25 SEQ ID NO: 304 is the determined cDNA sequence for clone #26993. SEQ ID NO: 305 is the determined cDNA sequence for clone #26994. SEQ ID NO: 306 is the determined cDNA sequence for clone #26995. SEQ ID NO: 307 is the determined cDNA sequence for clone #27003. 30 SEQ ID NO: 308 is the determined cDNA sequence for clone #27005. SEQ ID NO: 309 is the determined cDNA sequence for clone #27010.

SEQ ID NO: 310 is the determined cDNA sequence for clone #27011. SEQ ID NO: 311 is the determined cDNA sequence for clone #27013. SEQ ID NO: 312 is the determined cDNA sequence for clone #27016 SEQ ID NO: 313 is the determined cDNA sequence for clone #27017. 5 SEQ ID NO: 314 is the determined cDNA sequence for clone #27019. SEQ ID NO: 315 is the determined cDNA sequence for clone #27028. SEQ ID NO: 316 is the full-length cDNA sequence for clone #19060. SEQ ID NO: 317 is the full-length cDNA sequence for clone #18964. SEQ ID NO: 318 is the full-length cDNA sequence for clone #18929. SEQ ID NO: 319 is the full-length cDNA sequence for clone #18991. 10 SEQ ID NO: 320 is the full-length cDNA sequence for clone #18996. SEQ ID NO: 321 is the full-length cDNA sequence for clone #18966. SEO ID NO: 322 is the full-length cDNA sequence for clone #18951. SEO ID NO: 323 is the full-length cDNA sequence for clone #18973 (also known as L516S). 15 SEO ID NO: 324 is the amino acid sequence for clone #19060. SEQ ID NO: 325 is the amino acid sequence for clone #19063. SEQ ID NO: 326 is the amino acid sequence for clone #19077. SEQ ID NO: 327 is the amino acid sequence for clone #19110. SEQ ID NO: 328 is the amino acid sequence for clone #19122. 20 SEQ ID NO: 329 is the amino acid sequence for clone #19118. SEQ ID NO: 330 is the amino acid sequence for clone #19080. SEQ ID NO: 331 is the amino acid sequence for clone #19127. SEQ ID NO: 332 is the amino acid sequence for clone #19117. SEQ ID NO: 333 is the amino acid sequence for clone #19095, also 25 referred to L549S. SEQ ID NO: 334 is the amino acid sequence for clone #18964. SEQ ID NO: 335 is the amino acid sequence for clone #18929. SEQ ID NO: 336 is the amino acid sequence for clone #18991. 30 SEQ ID NO: 337 is the amino acid sequence for clone #18996. SEQ ID NO: 338 is the amino acid sequence for clone #18966.

SEQ ID NO: 339 is the amino acid sequence for clone #18951. SEQ ID NO: 340 is the amino acid sequence for clone #18973. SEQ ID NO: 341 is the determined cDNA sequence for clone 26461. SEQ ID NO: 342 is the determined cDNA sequence for clone 26462. 5 SEQ ID NO: 343 is the determined cDNA sequence for clone 26463. SEQ ID NO: 344 is the determined cDNA sequence for clone 26464. SEQ ID NO: 345 is the determined cDNA sequence for clone 26465. SEQ ID NO: 346 is the determined cDNA sequence for clone 26466. SEQ ID NO: 347 is the determined cDNA sequence for clone 26467. 10 SEO ID NO: 348 is the determined cDNA sequence for clone 26468. SEQ ID NO: 349 is the determined cDNA sequence for clone 26469. SEQ ID NO: 350 is the determined cDNA sequence for clone 26470. SEQ ID NO: 351 is the determined cDNA sequence for clone 26471. SEQ ID NO: 352 is the determined cDNA sequence for clone 26472. 15 SEQ ID NO: 353 is the determined cDNA sequence for clone 26474. SEQ ID NO: 354 is the determined cDNA sequence for clone 26475. SEO ID NO: 355 is the determined cDNA sequence for clone 26476. SEQ ID NO: 356 is the determined cDNA sequence for clone 26477. SEQ ID NO: 357 is the determined cDNA sequence for clone 26478. 20 SEQ ID NO: 358 is the determined cDNA sequence for clone 26479. SEO ID NO: 359 is the determined cDNA sequence for clone 26480. SEQ ID NO: 360 is the determined cDNA sequence for clone 26481. SEQ ID NO: 361 is the determined cDNA sequence for clone 26482 SEQ ID NO: 362 is the determined cDNA sequence for clone 26483. 25 SEQ ID NO: 363 is the determined cDNA sequence for clone 26484. SEQ ID NO: 364 is the determined cDNA sequence for clone 26485. SEQ ID NO: 365 is the determined cDNA sequence for clone 26486. SEQ ID NO: 366 is the determined cDNA sequence for clone 26487. SEQ ID NO: 367 is the determined cDNA sequence for clone 26488. 30 SEQ ID NO: 368 is the determined cDNA sequence for clone 26489. SEQ ID NO: 369 is the determined cDNA sequence for clone 26490.

SEQ ID NO: 370 is the determined cDNA sequence for clone 26491. SEQ ID NO: 371 is the determined cDNA sequence for clone 26492. SEQ ID NO: 372 is the determined cDNA sequence for clone 26493. SEQ ID NO: 373 is the determined cDNA sequence for clone 26494. 5 SEQ ID NO: 374 is the determined cDNA sequence for clone 26495. SEQ ID NO: 375 is the determined cDNA sequence for clone 26496. SEQ ID NO: 376 is the determined cDNA sequence for clone 26497. SEQ ID NO: 377 is the determined cDNA sequence for clone 26498. SEQ ID NO: 378 is the determined cDNA sequence for clone 26499. 10 SEQ ID NO: 379 is the determined cDNA sequence for clone 26500. SEQ ID NO: 380 is the determined cDNA sequence for clone 26501. SEQ ID NO: 381 is the determined cDNA sequence for clone 26502. SEQ ID NO: 382 is the determined cDNA sequence for clone 26503. SEQ ID NO: 383 is the determined cDNA sequence for clone 26504. SEQ ID NO: 384 is the determined cDNA sequence for clone 26505. 15 SEQ ID NO: 385 is the determined cDNA sequence for clone 26506. SEQ ID NO: 386 is the determined cDNA sequence for clone 26507. SEQ ID NO: 387 is the determined cDNA sequence for clone 26508. SEQ ID NO: 388 is the determined cDNA sequence for clone 26509. 20 SEQ ID NO: 389 is the determined cDNA sequence for clone 26511. SEQ ID NO: 390 is the determined cDNA sequence for clone 26513. SEQ ID NO: 391 is the determined cDNA sequence for clone 26514. SEQ ID NO: 392 is the determined cDNA sequence for clone 26515. SEQ ID NO: 393 is the determined cDNA sequence for clone 26516. 25 SEQ ID NO: 394 is the determined cDNA sequence for clone 26517. SEQ ID NO: 395 is the determined cDNA sequence for clone 26518. SEQ ID NO: 396 is the determined cDNA sequence for clone 26519. SEQ ID NO: 397 is the determined cDNA sequence for clone 26520. SEQ ID NO: 398 is the determined cDNA sequence for clone 26521. 30 SEQ ID NO: 399 is the determined cDNA sequence for clone 26522. SEQ ID NO: 400 is the determined cDNA sequence for clone 26523.

SEQ ID NO: 401 is the determined cDNA sequence for clone 26524. SEQ ID NO: 402 is the determined cDNA sequence for clone 26526. SEQ ID NO: 403 is the determined cDNA sequence for clone 26527. SEQ ID NO: 404 is the determined cDNA sequence for clone 26528. 5 SEQ ID NO: 405 is the determined cDNA sequence for clone 26529. SEQ ID NO: 406 is the determined cDNA sequence for clone 26530. SEQ ID NO: 407 is the determined cDNA sequence for clone 26532. SEQ ID NO: 408 is the determined cDNA sequence for clone 26533. SEQ ID NO: 409 is the determined cDNA sequence for clone 26534. 10 SEO ID NO: 410 is the determined cDNA sequence for clone 26535. SEQ ID NO: 411 is the determined cDNA sequence for clone 26536. SEQ ID NO: 412 is the determined cDNA sequence for clone 26537. SEQ ID NO: 413 is the determined cDNA sequence for clone 26538. SEQ ID NO: 414 is the determined cDNA sequence for clone 26540. 15 SEQ ID NO: 415 is the determined cDNA sequence for clone 26541. SEQ ID NO: 416 is the determined cDNA sequence for clone 26542. SEQ ID NO: 417 is the determined cDNA sequence for clone 26543. SEQ ID NO: 418 is the determined cDNA sequence for clone 26544. SEQ ID NO: 419 is the determined cDNA sequence for clone 26546. 20 SEQ ID NO: 420 is the determined cDNA sequence for clone 26547. SEQ ID NO: 421 is the determined cDNA sequence for clone 26548. SEQ ID NO: 422 is the determined cDNA sequence for clone 26549. SEQ ID NO: 423 is the determined cDNA sequence for clone 26550. SEQ ID NO: 424 is the determined cDNA sequence for clone 26551. 25 SEQ ID NO: 425 is the determined cDNA sequence for clone 26552. SEQ ID NO: 426 is the determined cDNA sequence for clone 26553. SEQ ID NO: 427 is the determined cDNA sequence for clone 26554. SEQ ID NO: 428 is the determined cDNA sequence for clone 26556. SEQ ID NO: 429 is the determined cDNA sequence for clone 26557. 30 SEQ ID NO: 430 is the determined cDNA sequence for clone 27631. SEQ ID NO: 431 is the determined cDNA sequence for clone 27632.

SEQ ID NO: 432 is the determined cDNA sequence for clone 27633. SEQ ID NO: 433 is the determined cDNA sequence for clone 27635. SEQ ID NO: 434 is the determined cDNA sequence for clone 27636. SEQ ID NO: 435 is the determined cDNA sequence for clone 27637. 5 SEQ ID NO: 436 is the determined cDNA sequence for clone 27638. SEQ ID NO: 437 is the determined cDNA sequence for clone 27639. SEQ ID NO: 438 is the determined cDNA sequence for clone 27640. SEQ ID NO: 439 is the determined cDNA sequence for clone 27641. SEQ ID NO: 440 is the determined cDNA sequence for clone 27642. SEQ ID NO: 441 is the determined cDNA sequence for clone 27644. 10 SEQ ID NO: 442 is the determined cDNA sequence for clone 27646. SEQ ID NO: 443 is the determined cDNA sequence for clone 27647. SEO ID NO: 444 is the determined cDNA sequence for clone 27649. SEQ ID NO: 445 is the determined cDNA sequence for clone 27650. SEO ID NO: 446 is the determined cDNA sequence for clone 27651. 15 SEQ ID NO: 447 is the determined cDNA sequence for clone 27652. SEO ID NO: 448 is the determined cDNA sequence for clone 27654. SEQ ID NO: 449 is the determined cDNA sequence for clone 27655. SEQ ID NO: 450 is the determined cDNA sequence for clone 27657. SEO ID NO: 451 is the determined cDNA sequence for clone 27659. 20 SEQ ID NO: 452 is the determined cDNA sequence for clone 27665. SEQ ID NO: 453 is the determined cDNA sequence for clone 27666. SEQ ID NO: 454 is the determined cDNA sequence for clone 27668. SEQ ID NO: 455 is the determined cDNA sequence for clone 27670. SEQ ID NO: 456 is the determined cDNA sequence for clone 27671. 25 SEQ ID NO: 457 is the determined cDNA sequence for clone 27672. SEO ID NO: 458 is the determined cDNA sequence for clone 27674. SEQ ID NO: 459 is the determined cDNA sequence for clone 27677. SEQ ID NO: 460 is the determined cDNA sequence for clone 27681. 30 SEQ ID NO: 461 is the determined cDNA sequence for clone 27682. SEQ ID NO: 462 is the determined cDNA sequence for clone 27683.

SEQ ID NO: 463 is the determined cDNA sequence for clone 27686. SEQ ID NO: 464 is the determined cDNA sequence for clone 27688. SEQ ID NO: 465 is the determined cDNA sequence for clone 27689. SEQ ID NO: 466 is the determined cDNA sequence for clone 27690. 5 SEQ ID NO: 467 is the determined cDNA sequence for clone 27693. SEQ ID NO: 468 is the determined cDNA sequence for clone 27699. SEQ ID NO: 469 is the determined cDNA sequence for clone 27700. SEQ ID NO: 470 is the determined cDNA sequence for clone 27702. SEQ ID NO: 471 is the determined cDNA sequence for clone 27705. 10 SEQ ID NO: 472 is the determined cDNA sequence for clone 27706. SEQ ID NO: 473 is the determined cDNA sequence for clone 27707. SEQ ID NO: 474 is the determined cDNA sequence for clone 27708. SEQ ID NO: 475 is the determined cDNA sequence for clone 27709. SEQ ID NO: 476 is the determined cDNA sequence for clone 27710. 15 SEQ ID NO: 477 is the determined cDNA sequence for clone 27711. SEQ ID NO: 478 is the determined cDNA sequence for clone 27712. SEQ ID NO: 479 is the determined cDNA sequence for clone 27713. SEQ ID NO: 480 is the determined cDNA sequence for clone 27714. SEQ ID NO: 481 is the determined cDNA sequence for clone 27715. 20 SEQ ID NO: 482 is the determined cDNA sequence for clone 27716. SEQ ID NO: 483 is the determined cDNA sequence for clone 27717. SEQ ID NO: 484 is the determined cDNA sequence for clone 27718. SEQ ID NO: 485 is the determined cDNA sequence for clone 27719. SEQ ID NO: 486 is the determined cDNA sequence for clone 27720. 25 SEQ ID NO: 487 is the determined cDNA sequence for clone 27722. SEQ ID NO: 488 is the determined cDNA sequence for clone 27723. SEQ ID NO: 489 is the determined cDNA sequence for clone 27724. SEQ ID NO: 490 is the determined cDNA sequence for clone 27726. SEQ ID NO: 491 is the determined cDNA sequence for clone 25015. 30 SEQ ID NO: 492 is the determined cDNA sequence for clone 25016. SEQ ID NO: 493 is the determined cDNA sequence for clone 25017.

SEQ ID NO: 494 is the determined cDNA sequence for clone 25018 SEQ ID NO: 495 is the determined cDNA sequence for clone 25030. SEQ ID NO: 496 is the determined cDNA sequence for clone 25033. SEQ ID NO: 497 is the determined cDNA sequence for clone 25034. 5 SEQ ID NO: 498 is the determined cDNA sequence for clone 25035. SEQ ID NO: 499 is the determined cDNA sequence for clone 25036. SEQ ID NO: 500 is the determined cDNA sequence for clone 25037. SEQ ID NO: 501 is the determined cDNA sequence for clone 25038. SEQ ID NO: 502 is the determined cDNA sequence for clone 25039. 10 SEQ ID NO: 503 is the determined cDNA sequence for clone 25040. SEQ ID NO: 504 is the determined cDNA sequence for clone 25042. SEQ ID NO: 505 is the determined cDNA sequence for clone 25043. SEQ ID NO: 506 is the determined cDNA sequence for clone 25044. SEQ ID NO: 507 is the determined cDNA sequence for clone 25045. SEQ ID NO: 508 is the determined cDNA sequence for clone 25047. 15 SEQ ID NO: 509 is the determined cDNA sequence for clone 25048. SEQ ID NO: 510 is the determined cDNA sequence for clone 25049. SEQ ID NO: 511 is the determined cDNA sequence for clone 25185. SEQ ID NO: 512 is the determined cDNA sequence for clone 25186. SEQ ID NO: 513 is the determined cDNA sequence for clone 25187. 20 SEO ID NO: 514 is the determined cDNA sequence for clone 25188. SEQ ID NO: 515 is the determined cDNA sequence for clone 25189. SEO ID NO: 516 is the determined cDNA sequence for clone 25190. SEQ ID NO: 517 is the determined cDNA sequence for clone 25193. SEQ ID NO: 518 is the determined cDNA sequence for clone 25194. 25 SEO ID NO: 519 is the determined cDNA sequence for clone 25196. SEQ ID NO: 520 is the determined cDNA sequence for clone 25198. SEQ ID NO: 521 is the determined cDNA sequence for clone 25199. SEQ ID NO: 522 is the determined cDNA sequence for clone 25200. 30 SEQ ID NO: 523 is the determined cDNA sequence for clone 25202. SEQ ID NO: 524 is the determined cDNA sequence for clone 25364.

SEQ ID NO: 525 is the determined cDNA sequence for clone 25366. SEQ ID NO: 526 is the determined cDNA sequence for clone 25367. SEQ ID NO: 527 is the determined cDNA sequence for clone 25368. SEQ ID NO: 528 is the determined cDNA sequence for clone 25369. SEQ ID NO: 529 is the determined cDNA sequence for clone 25370. 5 SEQ ID NO: 530 is the determined cDNA sequence for clone 25371. SEQ ID NO: 531 is the determined cDNA sequence for clone 25372. SEQ ID NO: 532 is the determined cDNA sequence for clone 25373. SEQ ID NO: 533 is the determined cDNA sequence for clone 25374. 10 SEQ ID NO: 534 is the determined cDNA sequence for clone 25376. SEQ ID NO: 535 is the determined cDNA sequence for clone 25377. SEQ ID NO: 536 is the determined cDNA sequence for clone 25378. SEQ ID NO: 537 is the determined cDNA sequence for clone 25379. SEQ ID NO: 538 is the determined cDNA sequence for clone 25380. 15 SEQ ID NO: 539 is the determined cDNA sequence for clone 25381. SEQ ID NO: 540 is the determined cDNA sequence for clone 25382. SEQ ID NO: 541 is the determined cDNA sequence for clone 25383. SEQ ID NO: 542 is the determined cDNA sequence for clone 25385. SEQ ID NO: 543 is the determined cDNA sequence for clone 25386. 20 SEQ ID NO: 544 is the determined cDNA sequence for clone 25387. SEQ ID NO: 545 is the determined cDNA sequence for clone 26013. SEQ ID NO: 546 is the determined cDNA sequence for clone 26014. SEQ ID NO: 547 is the determined cDNA sequence for clone 26016. SEQ ID NO: 548 is the determined cDNA sequence for clone 26017. 25 SEQ ID NO: 549 is the determined cDNA sequence for clone 26018. SEQ ID NO: 550 is the determined cDNA sequence for clone 26019. SEQ ID NO: 551 is the determined cDNA sequence for clone 26020. SEQ ID NO: 552 is the determined cDNA sequence for clone 26021. SEQ ID NO: 553 is the determined cDNA sequence for clone 26022. 30 SEQ ID NO: 554 is the determined cDNA sequence for clone 26027. SEQ ID NO: 555 is the determined cDNA sequence for clone 26197.

SEQ ID NO: 556 is the determined cDNA sequence for clone 26199. SEQ ID NO: 557 is the determined cDNA sequence for clone 26201. SEQ ID NO: 558 is the determined cDNA sequence for clone 26202. SEQ ID NO: 559 is the determined cDNA sequence for clone 26203. 5 SEQ ID NO: 560 is the determined cDNA sequence for clone 26204. SEQ ID NO: 561 is the determined cDNA sequence for clone 26205. SEQ ID NO: 562 is the determined cDNA sequence for clone 26206. SEQ ID NO: 563 is the determined cDNA sequence for clone 26208. SEQ ID NO: 564 is the determined cDNA sequence for clone 26211. 10 SEQ ID NO: 565 is the determined cDNA sequence for clone 26212. SEQ ID NO: 566 is the determined cDNA sequence for clone 26213. SEQ ID NO: 567 is the determined cDNA sequence for clone 26214. SEO ID NO: 568 is the determined cDNA sequence for clone 26215. SEO ID NO: 569 is the determined cDNA sequence for clone 26216. SEO ID NO: 570 is the determined cDNA sequence for clone 26217. 15 SEQ ID NO: 571 is the determined cDNA sequence for clone 26218. SEQ ID NO: 572 is the determined cDNA sequence for clone 26219. SEO ID NO: 573 is the determined cDNA sequence for clone 26220. SEQ ID NO: 574 is the determined cDNA sequence for clone 26221. SEQ ID NO: 575 is the determined cDNA sequence for clone 26224. 20 SEQ ID NO: 576 is the determined cDNA sequence for clone 26225. SEQ ID NO: 577 is the determined cDNA sequence for clone 26226. SEQ ID NO: 578 is the determined cDNA sequence for clone 26227. SEQ ID NO: 579 is the determined cDNA sequence for clone 26228. SEO ID NO: 580 is the determined cDNA sequence for clone 26230. 25 SEQ ID NO: 581 is the determined cDNA sequence for clone 26231. SEO ID NO: 582 is the determined cDNA sequence for clone 26234. SEQ ID NO: 583 is the determined cDNA sequence for clone 26236. SEO ID NO: 584 is the determined cDNA sequence for clone 26237. 30 SEQ ID NO: 585 is the determined cDNA sequence for clone 26239. SEQ ID NO: 586 is the determined cDNA sequence for clone 26240.

SEQ ID NO: 587 is the determined cDNA sequence for clone 26241. SEQ ID NO: 588 is the determined cDNA sequence for clone 26242. SEQ ID NO: 589 is the determined cDNA sequence for clone 26246. SEQ ID NO: 590 is the determined cDNA sequence for clone 26247. 5 SEQ ID NO: 591 is the determined cDNA sequence for clone 26248. SEQ ID NO: 592 is the determined cDNA sequence for clone 26249. SEQ ID NO: 593 is the determined cDNA sequence for clone 26250. SEQ ID NO: 594 is the determined cDNA sequence for clone 26251. SEQ ID NO: 595 is the determined cDNA sequence for clone 26252. 10 SEQ ID NO: 596 is the determined cDNA sequence for clone 26253. SEQ ID NO: 597 is the determined cDNA sequence for clone 26254. SEQ ID NO: 598 is the determined cDNA sequence for clone 26255. SEQ ID NO: 599 is the determined cDNA sequence for clone 26256. SEQ ID NO: 600 is the determined cDNA sequence for clone 26257. SEQ ID NO: 601 is the determined cDNA sequence for clone 26259. 15 SEQ ID NO: 602 is the determined cDNA sequence for clone 26260. SEQ ID NO: 603 is the determined cDNA sequence for clone 26261. SEQ ID NO: 604 is the determined cDNA sequence for clone 26262. SEQ ID NO: 605 is the determined cDNA sequence for clone 26263. 20 SEQ ID NO: 606 is the determined cDNA sequence for clone 26264. SEQ ID NO: 607 is the determined cDNA sequence for clone 26265. SEQ ID NO: 608 is the determined cDNA sequence for clone 26266. SEQ ID NO: 609 is the determined cDNA sequence for clone 26268. SEQ ID NO: 610 is the determined cDNA sequence for clone 26269. SEQ ID NO: 611 is the determined cDNA sequence for clone 26271. 25 SEQ ID NO: 612 is the determined cDNA sequence for clone 26273. SEQ ID NO: 613 is the determined cDNA sequence for clone 26810. SEQ ID NO: 614 is the determined cDNA sequence for clone 26811. SEQ ID NO: 615 is the determined cDNA sequence for clone 26812.1. 30 SEQ ID NO: 616 is the determined cDNA sequence for clone 26812.2. SEQ ID NO: 617 is the determined cDNA sequence for clone 26813.

SEQ ID NO: 618 is the determined cDNA sequence for clone 26814. SEQ ID NO: 619 is the determined cDNA sequence for clone 26815. SEQ ID NO: 620 is the determined cDNA sequence for clone 26816. SEQ ID NO: 621 is the determined cDNA sequence for clone 26818. 5 SEQ ID NO: 622 is the determined cDNA sequence for clone 26819. SEQ ID NO: 623 is the determined cDNA sequence for clone 26820. SEQ ID NO: 624 is the determined cDNA sequence for clone 26821. SEQ ID NO: 625 is the determined cDNA sequence for clone 26822. SEQ ID NO: 626 is the determined cDNA sequence for clone 26824. 10 SEQ ID NO: 627 is the determined cDNA sequence for clone 26825. SEQ ID NO: 628 is the determined cDNA sequence for clone 26826. SEQ ID NO: 629 is the determined cDNA sequence for clone 26827. SEQ ID NO: 630 is the determined cDNA sequence for clone 26829. SEQ ID NO: 631 is the determined cDNA sequence for clone 26830. 15 SEQ ID NO: 632 is the determined cDNA sequence for clone 26831. SEQ ID NO: 633 is the determined cDNA sequence for clone 26832. SEQ ID NO: 634 is the determined cDNA sequence for clone 26835. SEO ID NO: 635 is the determined cDNA sequence for clone 26836. SEQ ID NO: 636 is the determined cDNA sequence for clone 26837. 20 SEQ ID NO: 637 is the determined cDNA sequence for clone 26839. SEQ ID NO: 638 is the determined cDNA sequence for clone 26841. SEQ ID NO: 639 is the determined cDNA sequence for clone 26843. SEQ ID NO: 640 is the determined cDNA sequence for clone 26844. SEQ ID NO: 641 is the determined cDNA sequence for clone 26845. 25 SEQ ID NO: 642 is the determined cDNA sequence for clone 26846. SEQ ID NO: 643 is the determined cDNA sequence for clone 26847. SEQ ID NO: 644 is the determined cDNA sequence for clone 26848. SEQ ID NO: 645 is the determined cDNA sequence for clone 26849. SEQ ID NO: 646 is the determined cDNA sequence for clone 26850. 30 SEQ ID NO: 647 is the determined cDNA sequence for clone 26851. SEQ ID NO: 648 is the determined cDNA sequence for clone 26852.

SEQ ID NO: 649 is the determined cDNA sequence for clone 26853. SEQ ID NO: 650 is the determined cDNA sequence for clone 26854. SEQ ID NO: 651 is the determined cDNA sequence for clone 26856. SEQ ID NO: 652 is the determined cDNA sequence for clone 26857. 5 SEQ ID NO: 653 is the determined cDNA sequence for clone 26858. SEQ ID NO: 654 is the determined cDNA sequence for clone 26859. SEQ ID NO: 655 is the determined cDNA sequence for clone 26860. SEQ ID NO: 656 is the determined cDNA sequence for clone 26862. SEQ ID NO: 657 is the determined cDNA sequence for clone 26863. 10 SEQ ID NO: 658 is the determined cDNA sequence for clone 26864. SEQ ID NO: 659 is the determined cDNA sequence for clone 26865. SEQ ID NO: 660 is the determined cDNA sequence for clone 26867. SEQ ID NO: 661 is the determined cDNA sequence for clone 26868. SEQ ID NO: 662 is the determined cDNA sequence for clone 26871. SEQ ID NO: 663 is the determined cDNA sequence for clone 26873. 15 SEQ ID NO: 664 is the determined cDNA sequence for clone 26875. SEQ ID NO: 665 is the determined cDNA sequence for clone 26876. SEQ ID NO: 666 is the determined cDNA sequence for clone 26877. SEQ ID NO: 667 is the determined cDNA sequence for clone 26878. 20 SEQ ID NO: 668 is the determined cDNA sequence for clone 26880. SEQ ID NO: 669 is the determined cDNA sequence for clone 26882. SEQ ID NO: 670 is the determined cDNA sequence for clone 26883. SEQ ID NO: 671 is the determined cDNA sequence for clone 26884. SEQ ID NO: 672 is the determined cDNA sequence for clone 26885. 25 SEQ ID NO: 673 is the determined cDNA sequence for clone 26886. SEQ ID NO: 674 is the determined cDNA sequence for clone 26887. SEQ ID NO: 675 is the determined cDNA sequence for clone 26888. SEQ ID NO: 676 is the determined cDNA sequence for clone 26889. SEQ ID NO: 677 is the determined cDNA sequence for clone 26890. 30 SEQ ID NO: 678 is the determined cDNA sequence for clone 26892. SEQ ID NO: 679 is the determined cDNA sequence for clone 26894.

SEQ ID NO: 680 is the determined cDNA sequence for clone 26895. SEQ ID NO: 681 is the determined cDNA sequence for clone 26897. SEQ ID NO: 682 is the determined cDNA sequence for clone 26898. SEQ ID NO: 683 is the determined cDNA sequence for clone 26899. 5 SEQ ID NO: 684 is the determined cDNA sequence for clone 26900. SEQ ID NO: 685 is the determined cDNA sequence for clone 26901. SEQ ID NO: 686 is the determined cDNA sequence for clone 26903. SEQ ID NO: 687 is the determined cDNA sequence for clone 26905. SEQ ID NO: 688 is the determined cDNA sequence for clone 26906. 10 SEQ ID NO: 689 is the determined cDNA sequence for clone 26708. SEQ ID NO: 690 is the determined cDNA sequence for clone 26709. SEQ ID NO: 691 is the determined cDNA sequence for clone 26710. SEQ ID NO: 692 is the determined cDNA sequence for clone 26711. SEQ ID NO: 693 is the determined cDNA sequence for clone 26712. 15 SEQ ID NO: 694 is the determined cDNA sequence for clone 26713. SEQ ID NO: 695 is the determined cDNA sequence for clone 26714. SEQ ID NO: 696 is the determined cDNA sequence for clone 26715. SEQ ID NO: 697 is the determined cDNA sequence for clone 26716. SEO ID NO: 698 is the determined cDNA sequence for clone 26717. 20 SEQ ID NO: 699 is the determined cDNA sequence for clone 26718. SEQ ID NO: 700 is the determined cDNA sequence for clone 26719. SEQ ID NO: 701 is the determined cDNA sequence for clone 26720. SEQ ID NO: 702 is the determined cDNA sequence for clone 26721. SEQ ID NO: 703 is the determined cDNA sequence for clone 26722. 25 SEQ ID NO: 704 is the determined cDNA sequence for clone 26723. SEQ ID NO: 705 is the determined cDNA sequence for clone 26724. SEO ID NO: 706 is the determined cDNA sequence for clone 26725. SEQ ID NO: 707 is the determined cDNA sequence for clone 26726. SEQ ID NO: 708 is the determined cDNA sequence for clone 26727. 30 SEQ ID NO: 709 is the determined cDNA sequence for clone 26728. SEQ ID NO: 710 is the determined cDNA sequence for clone 26729.

	SEQ ID NO: 711 is the determined cDNA sequence for clone 26730.
	SEQ ID NO: 712 is the determined cDNA sequence for clone 26731.
	SEQ ID NO: 713 is the determined cDNA sequence for clone 26732.
	SEQ ID NO: 714 is the determined cDNA sequence for clone 26733.1.
5	SEQ ID NO: 715 is the determined cDNA sequence for clone 26733.2.
	SEQ ID NO: 716 is the determined cDNA sequence for clone 26734.
	SEQ ID NO: 717 is the determined cDNA sequence for clone 26735.
	SEQ ID NO: 718 is the determined cDNA sequence for clone 26736.
	SEQ ID NO: 719 is the determined cDNA sequence for clone 26737.
10	SEQ ID NO: 720 is the determined cDNA sequence for clone 26738.
	SEQ ID NO: 721 is the determined cDNA sequence for clone 26739.
	SEQ ID NO: 722 is the determined cDNA sequence for clone 26741.
	SEQ ID NO: 723 is the determined cDNA sequence for clone 26742.
	SEQ ID NO: 724 is the determined cDNA sequence for clone 26743.
15	SEQ ID NO: 725 is the determined cDNA sequence for clone 26744.
	SEQ ID NO: 726 is the determined cDNA sequence for clone 26745.
	SEQ ID NO: 727 is the determined cDNA sequence for clone 26746.
	SEQ ID NO: 728 is the determined cDNA sequence for clone 26747.
	SEQ ID NO: 729 is the determined cDNA sequence for clone 26748.
20	SEQ ID NO: 730 is the determined cDNA sequence for clone 26749.
	SEQ ID NO: 731 is the determined cDNA sequence for clone 26750.
	SEQ ID NO: 732 is the determined cDNA sequence for clone 26751.
	SEQ ID NO: 733 is the determined cDNA sequence for clone 26752.
	SEQ ID NO: 734 is the determined cDNA sequence for clone 26753.
25	SEQ ID NO: 735 is the determined cDNA sequence for clone 26754.
	SEQ ID NO: 736 is the determined cDNA sequence for clone 26755.
·	SEQ ID NO: 737 is the determined cDNA sequence for clone 26756.
	SEQ ID NO: 738 is the determined cDNA sequence for clone 26757.
	SEQ ID NO: 739 is the determined cDNA sequence for clone 26758.
30	SEQ ID NO: 740 is the determined cDNA sequence for clone 26759.
	SEQ ID NO: 741 is the determined cDNA sequence for clone 26760.

	SEQ ID NO: 742 is the determined cDNA sequence for clone 26761.
	SEQ ID NO: 743 is the determined cDNA sequence for clone 26762.
	SEQ ID NO: 744 is the determined cDNA sequence for clone 26763.
	SEQ ID NO: 745 is the determined cDNA sequence for clone 26764.
5	SEQ ID NO: 746 is the determined cDNA sequence for clone 26765.
	SEQ ID NO: 747 is the determined cDNA sequence for clone 26766.
	SEQ ID NO: 748 is the determined cDNA sequence for clone 26767.
	SEQ ID NO: 749 is the determined cDNA sequence for clone 26768.
	SEQ ID NO: 750 is the determined cDNA sequence for clone 26769.
10	SEQ ID NO: 751 is the determined cDNA sequence for clone 26770.
	SEQ ID NO: 752 is the determined cDNA sequence for clone 26771.
	SEQ ID NO: 753 is the determined cDNA sequence for clone 26772.
	SEQ ID NO: 754 is the determined cDNA sequence for clone 26773.
•	SEQ ID NO: 755 is the determined cDNA sequence for clone 26774.
15	SEQ ID NO: 756 is the determined cDNA sequence for clone 26775.
	SEQ ID NO: 757 is the determined cDNA sequence for clone 26776.
	SEQ ID NO: 758 is the determined cDNA sequence for clone 26777.
	SEQ ID NO: 759 is the determined cDNA sequence for clone 26778.
	SEQ ID NO: 760 is the determined cDNA sequence for clone 26779.
20	SEQ ID NO: 761 is the determined cDNA sequence for clone 26781.
	SEQ ID NO: 762 is the determined cDNA sequence for clone 26782.
	SEQ ID NO: 763 is the determined cDNA sequence for clone 26783.
	SEQ ID NO: 764 is the determined cDNA sequence for clone 26784.
	SEQ ID NO: 765 is the determined cDNA sequence for clone 26785.
25	SEQ ID NO: 766 is the determined cDNA sequence for clone 26786.
	SEQ ID NO: 767 is the determined cDNA sequence for clone 26787.
	SEQ ID NO: 768 is the determined cDNA sequence for clone 26788.
	SEQ ID NO: 769 is the determined cDNA sequence for clone 26790.
	SEQ ID NO: 770 is the determined cDNA sequence for clone 26791.
30	SEQ ID NO: 771 is the determined cDNA sequence for clone 26792.
	SEQ ID NO: 772 is the determined cDNA sequence for clone 26793.

SEQ ID NO: 773 is the determined cDNA sequence for clone 26794.

SEQ ID NO: 774 is the determined cDNA sequence for clone 26795.

SEQ ID NO: 775 is the determined cDNA sequence for clone 26796.

SEQ ID NO: 776 is the determined cDNA sequence for clone 26797.

SEQ ID NO: 777 is the determined cDNA sequence for clone 26798.

SEQ ID NO: 778 is the determined cDNA sequence for clone 26800.

SEQ ID NO: 779 is the determined cDNA sequence for clone 26801.

SEQ ID NO: 780 is the determined cDNA sequence for clone 26802.

SEQ ID NO: 781 is the determined cDNA sequence for clone 26803.

SEQ ID NO: 782 is the determined cDNA sequence for clone 26804.

SEQ ID NO: 783 is the amino acid sequence for L773P.

SEQ ID NO: 784 is the determined DNA sequence of the L773P expression construct.

SEQ ID NO: 785 is the determined DNA sequence of the L773PA expression construct.

SEQ ID NO: 786 is a predicted amino acid sequence for L552S.

SEQ ID NO: 787 is a predicted amino acid sequence for L840P.

SEQ ID NO: 788 is the full-length cDNA sequence for L548S.

SEQ ID NO: 789 is the amino acid sequence encoded by SEQ ID NO:

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SEQ ID NO: 790 is an extended cDNA sequence for L552S.

SEQ ID NO: 791 is the predicted amino acid sequence encoded by the cDNA sequence of SEQ ID NO: 790.

SEQ ID NO: 792 is the determined cDNA sequence for an isoform of

25 L552S.

SEQ ID NO: 793 is the predicted amino acid sequence encoded by SEQ ID NO: 792.

SEQ ID NO: 794 is an extended cDNA sequence for L840P.

SEQ ID NO: 795 is the predicted amino acid sequence encoded by SEQ

30 DI NO: 794.

SEQ ID NO: 796 is an extended cDNA sequence for L801P.

SEQ ID NO: 797 is a first predicted amino acid sequence encoded by SEQ ID NO: 796.

SEQ ID NO: 798 is a second predicted amino acid sequence encoded by SEQ ID NO: 796.

SEQ ID NO: 799 is a third predicted amino acid sequence encoded by SEQ ID NO: 796.

SEQ ID NO: 800 is the determined full-length sequence for L844P.

SEQ ID NO: 801 is the 5' consensus cDNA sequence for L551S.

SEQ ID NO: 802 is the 3' consensus cDNA sequence for L551S.

SEQ ID NO: 803 is the cDNA sequence for STY8.

SEQ ID NO: 804 is an extended cDNA sequence for L551S.

SEQ ID NO: 805 is the amino acid sequence for STY8.

SEQ ID NO: 806 is the extended amino acid sequence for L551S.

SEQ ID NO: 807 is the determined full-length cDNA sequence for

15 L773P.

SEQ ID NO: 808 is the full-length cDNA sequence of L552S.

SEQ ID NO: 809 is the full-length amino acid sequence of L552S.

SEQ ID NO: 810 is the determined cDNA sequence of clone 50989.

SEQ ID NO: 811 is the determined cDNA sequence of clone 50990.

SEQ ID NO: 812 is the determined cDNA sequence of clone 50992.

SEQ ID NO: 813-824 are the determined cDNA sequences for clones isolated from lung tumor tissue.

SEQ ID NO: 825 is the determined cDNA sequence for the full-length L551S clone 54305.

SEQ ID NO: 826 is the determined cDNA sequence for the full-length L551S clone 54298.

SEQ ID NO: 827 is the full-length amino acid sequence for L551S.

DETAILED DESCRIPTION OF THE INVENTION

As noted above, the present invention is generally directed to compositions and methods for using the compositions, for example in the therapy and diagnosis of cancer, such as lung cancer. Certain illustrative compositions described herein include lung tumor polypeptides, polynucleotides encoding such polypeptides, binding agents such as antibodies, antigen presenting cells (APCs) and/or immune system cells (e.g., T cells). A " lung tumor protein," as the term is used herein, refers generally to a protein that is expressed in lung tumor cells at a level that is at least two fold, and preferably at least five fold, greater than the level of expression in a normal tissue, as determined using a representative assay provided herein. Certain lung tumor proteins are tumor proteins that react detectably (within an immunoassay, such as an ELISA or Western blot) with antisera of a patient afflicted with lung cancer.

Therefore, in accordance with the above, and as described further below, the present invention provides illustrative polynucleotide compositions having 15 sequences set forth in SEQ ID NO: 1, 11-13, 15, 20, 23-27, 29, 30, 33, 34, 39, 41, 43-46, 51, 52, 57, 58, 60, 62, 65-67, 69-71, 74, 76, 79, 80, 84, 86, 89-92, 95, 97, 98, 101, 110, 111, 113-119, 121-128, 130-134, 136, 138, 139, 141, 143, 146-151, 153, 154, 157-160, 162-164, 167-178, 180, 181, 183, 186-190, 192, 193, 195-220, 224, 226-231, 234, 236, 237, 240, 241, 244-246, 248, 254, 255, 261, 262, 266, 270, 275, 280, 282, 283, 20 288, 289, 290, 292, 295, 301, 303, 304, 309, 311, 341-782, 784, 785, 790, 792, 794, 796, 800-804, 807, 808 and 810-826, illustrative polypeptide compositions having amino acid sequences set forth in SEQ ID NO: 786, 787, 791, 793, 795, 797-799, 806, 809 and 827, antibody compositions capable of binding such polypeptides, and numerous additional embodiments employing such compositions, for example in the 25 detection, diagnosis and/or therapy of human lung cancer.

POLYNUCLEOTIDE COMPOSITIONS

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As used herein, the terms "DNA segment" and "polynucleotide" refer to a DNA molecule that has been isolated free of total genomic DNA of a particular species. Therefore, a DNA segment encoding a polypeptide refers to a DNA segment that contains one or more coding sequences yet is substantially isolated away from, or

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purified free from, total genomic DNA of the species from which the DNA segment is obtained. Included within the terms "DNA segment" and "polynucleotide" are DNA segments and smaller fragments of such segments, and also recombinant vectors, including, for example, plasmids, cosmids, phagemids, phage, viruses, and the like.

As will be understood by those skilled in the art, the DNA segments of this invention can include genomic sequences, extra-genomic and plasmid-encoded sequences and smaller engineered gene segments that express, or may be adapted to express, proteins, polypeptides, peptides and the like. Such segments may be naturally isolated, or modified synthetically by the hand of man.

"Isolated," as used herein, means that a polynucleotide is substantially away from other coding sequences, and that the DNA segment does not contain large portions of unrelated coding DNA, such as large chromosomal fragments or other functional genes or polypeptide coding regions. Of course, this refers to the DNA segment as originally isolated, and does not exclude genes or coding regions later added to the segment by the hand of man.

As will be recognized by the skilled artisan, polynucleotides may be single-stranded (coding or antisense) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. RNA molecules include HnRNA molecules, which contain introns and correspond to a DNA molecule in a one-to-one manner, and mRNA molecules, which do not contain introns. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide of the present invention, and a polynucleotide may, but need not, be linked to other molecules and/or support materials.

Polynucleotides may comprise a native sequence (i.e., an endogenous sequence that encodes a lung tumor protein or a portion thereof) or may comprise a variant, or a biological or antigenic functional equivalent of such a sequence. Polynucleotide variants may contain one or more substitutions, additions, deletions and/or insertions, as further described below, preferably such that the immunogenicity of the encoded polypeptide is not diminished, relative to a native tumor protein. The effect on the immunogenicity of the encoded polypeptide may generally be assessed as

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described herein. The term "variants" also encompasses homologous genes of xenogenic origin.

When comparing polynucleotide or polypeptide sequences, two sequences are said to be "identical" if the sequence of nucleotides or amino acids in the two sequences is the same when aligned for maximum correspondence, as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships. In Dayhoff, M.O. (ed.) Atlas of Protein Sequence and Structure, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenes pp. 626-645 *Methods in Enzymology* vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) *CABIOS 5*:151-153; Myers, E.W. and Muller W. (1988) *CABIOS 4*:11-17; Robinson, E.D. (1971) *Comb. Theor 11*:105; Santou, N. Nes, M. (1987) *Mol. Biol. Evol. 4*:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) *Numerical Taxonomy – the Principles and Practice of Numerical Taxonomy*, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) *Proc. Natl. Acad., Sci. USA 80*:726-730.

Alternatively, optimal alignment of sequences for comparison may be conducted by the local identity algorithm of Smith and Waterman (1981) Add. APL. Math 2:482, by the identity alignment algorithm of Needleman and Wunsch (1970) J. Mol. Biol. 48:443, by the search for similarity methods of Pearson and Lipman (1988) Proc. Natl. Acad. Sci. USA 85: 2444, by computerized implementations of these algorithms (GAP, BESTFIT, BLAST, FASTA, and TFASTA in the Wisconsin Genetics

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Software Package, Genetics Computer Group (GCG), 575 Science Dr., Madison, WI), or by inspection.

One preferred example of algorithms that are suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul et al. (1977) Nucl. Acids Res. 25:3389-3402 and Altschul et al. (1990) J. Mol. Biol. 215:403-410, respectively. BLAST and BLAST 2.0 can be used, for example with the parameters described herein, to determine percent sequence identity for the polynucleotides and polypeptides of the invention. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information. In one illustrative example, cumulative scores can be calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always >0) and N (penalty score for mismatching residues; always For amino acid sequences, a scoring matrix can be used to calculate the <0). cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (W) of 11, and expectation (E) of 10, and the BLOSUM62 scoring matrix (see Henikoff and Henikoff (1989) Proc. Natl. Acad. Sci. USA 89:10915) alignments, (B) of 50, expectation (E) of 10, M=5, N=-4 and a comparison of both strands.

Preferably, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polynucleotide or polypeptide sequence in the comparison window may comprise additions or deletions (*i.e.*, gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid bases or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the

total number of positions in the reference sequence (i.e., the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

Therefore, the present invention encompasses polynucleotide and polypeptide sequences having substantial identity to the sequences disclosed herein, for example those comprising at least 50% sequence identity, preferably at least 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% or higher, sequence identity compared to a polynucleotide or polypeptide sequence of this invention using the methods described herein, (e.g., BLAST analysis using standard parameters, as described below). One skilled in this art will recognize that these values can be appropriately adjusted to determine corresponding identity of proteins encoded by two nucleotide sequences by taking into account codon degeneracy, amino acid similarity, reading frame positioning and the like.

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In additional embodiments, the present invention provides isolated polynucleotides and polypeptides comprising various lengths of contiguous stretches of sequence identical to or complementary to one or more of the sequences disclosed herein. For example, polynucleotides are provided by this invention that comprise at least about 15, 20, 30, 40, 50, 75, 100, 150, 200, 300, 400, 500 or 1000 or more contiguous nucleotides of one or more of the sequences disclosed herein as well as all intermediate lengths there between. It will be readily understood that "intermediate lengths", in this context, means any length between the quoted values, such as 16, 17, 18, 19, etc.; 21, 22, 23, etc.; 30, 31, 32, etc.; 50, 51, 52, 53, etc.; 100, 101, 102, 103, etc.; 150, 151, 152, 153, etc.; including all integers through 200-500; 500-1,000, and the like.

The polynucleotides of the present invention, or fragments thereof, regardless of the length of the coding sequence itself, may be combined with other DNA sequences, such as promoters, polyadenylation signals, additional restriction enzyme sites, multiple cloning sites, other coding segments, and the like, such that their overall length may vary considerably. It is therefore contemplated that a nucleic acid fragment of almost any length may be employed, with the total length preferably being limited by the ease of preparation and use in the intended recombinant DNA protocol. For example, illustrative DNA segments with total lengths of about 10,000, about 5000,

about 3000, about 2,000, about 1,000, about 500, about 200, about 100, about 50 base pairs in length, and the like, (including all intermediate lengths) are contemplated to be useful in many implementations of this invention.

In other embodiments, the present invention is directed to polynucleotides that are capable of hybridizing under moderately stringent conditions to a polynucleotide sequence provided herein, or a fragment thereof, or a complementary sequence thereof. Hybridization techniques are well known in the art of molecular biology. For purposes of illustration, suitable moderately stringent conditions for testing the hybridization of a polynucleotide of this invention with other polynucleotides include prewashing in a solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-65°C, 5 X SSC, overnight; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS.

Moreover, it will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that encode a polypeptide as described herein. Some of these polynucleotides bear minimal homology to the nucleotide sequence of any native gene. Nonetheless, polynucleotides that vary due to differences in codon usage are specifically contemplated by the present invention. Further, alleles of the genes comprising the polynucleotide sequences provided herein are within the scope of the present invention. Alleles are endogenous genes that are altered as a result of one or more mutations, such as deletions, additions and/or substitutions of nucleotides. The resulting mRNA and protein may, but need not, have an altered structure or function. Alleles may be identified using standard techniques (such as hybridization, amplification and/or database sequence comparison).

PROBES AND PRIMERS

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In other embodiments of the present invention, the polynucleotide sequences provided herein can be advantageously used as probes or primers for nucleic acid hybridization. As such, it is contemplated that nucleic acid segments that comprise a sequence region of at least about 15 nucleotide long contiguous sequence that has the

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same sequence as, or is complementary to, a 15 nucleotide long contiguous sequence disclosed herein will find particular utility. Longer contiguous identical or complementary sequences, e.g., those of about 20, 30, 40, 50, 100, 200, 500, 1000 (including all intermediate lengths) and even up to full length sequences will also be of use in certain embodiments.

The ability of such nucleic acid probes to specifically hybridize to a sequence of interest will enable them to be of use in detecting the presence of complementary sequences in a given sample. However, other uses are also envisioned, such as the use of the sequence information for the preparation of mutant species primers, or primers for use in preparing other genetic constructions.

Polynucleotide molecules having sequence regions consisting of contiguous nucleotide stretches of 10-14, 15-20, 30, 50, or even of 100-200 nucleotides or so (including intermediate lengths as well), identical or complementary to a polynucleotide sequence disclosed herein, are particularly contemplated as hybridization probes for use in, e.g., Southern and Northern blotting. This would allow a gene product, or fragment thereof, to be analyzed, both in diverse cell types and also in various bacterial cells. The total size of fragment, as well as the size of the complementary stretch(es), will ultimately depend on the intended use or application of the particular nucleic acid segment. Smaller fragments will generally find use in hybridization embodiments, wherein the length of the contiguous complementary region may be varied, such as between about 15 and about 100 nucleotides, but larger contiguous complementarity stretches may be used, according to the length complementary sequences one wishes to detect.

The use of a hybridization probe of about 15-25 nucleotides in length allows the formation of a duplex molecule that is both stable and selective. Molecules having contiguous complementary sequences over stretches greater than 15 bases in length are generally preferred, though, in order to increase stability and selectivity of the hybrid, and thereby improve the quality and degree of specific hybrid molecules obtained. One will generally prefer to design nucleic acid molecules having genecomplementary stretches of 15 to 25 contiguous nucleotides, or even longer where desired.

Hybridization probes may be selected from any portion of any of the sequences disclosed herein. All that is required is to review the sequence set forth in SEQ ID NO: 1, 11-13, 15, 20, 23-27, 29, 30, 33, 34, 39, 41, 43-46, 51, 52, 57, 58, 60, 62, 65-67, 69-71, 74, 76, 79, 80, 84, 86, 89-92, 95, 97, 98, 101, 110, 111, 113-119, 121-128, 130-134, 136, 138, 139, 141, 143, 146-151, 153, 154, 157-160, 162-164, 167-178, 180, 181, 183, 186-190, 192, 193, 195-220, 224, 226-231, 234, 236, 237, 240, 241, 244-246, 248, 254, 255, 261, 262, 266, 270, 275, 280, 282, 283, 288, 289, 290, 292, 295, 301, 303, 304, 309, 311, 341-782, 784, 785, 790, 792, 794, 796, 800-804, 807, 808 and 810-826, or to any continuous portion of the sequence, from about 15-25 nucleotides in length up to and including the full length sequence, that one wishes to utilize as a probe or primer. The choice of probe and primer sequences may be governed by various factors. For example, one may wish to employ primers from towards the termini of the total sequence.

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Small polynucleotide segments or fragments may be readily prepared by, for example, directly synthesizing the fragment by chemical means, as is commonly practiced using an automated oligonucleotide synthesizer. Also, fragments may be obtained by application of nucleic acid reproduction technology, such as the PCRTM technology of U. S. Patent 4,683,202 (incorporated herein by reference), by introducing selected sequences into recombinant vectors for recombinant production, and by other recombinant DNA techniques generally known to those of skill in the art of molecular biology.

The nucleotide sequences of the invention may be used for their ability to selectively form duplex molecules with complementary stretches of the entire gene or gene fragments of interest. Depending on the application envisioned, one will typically desire to employ varying conditions of hybridization to achieve varying degrees of selectivity of probe towards target sequence. For applications requiring high selectivity, one will typically desire to employ relatively stringent conditions to form the hybrids, e.g., one will select relatively low salt and/or high temperature conditions, such as provided by a salt concentration of from about 0.02 M to about 0.15 M salt at temperatures of from about 50°C to about 70°C. Such selective conditions tolerate

little, if any, mismatch between the probe and the template or target strand, and would be particularly suitable for isolating related sequences.

Of course, for some applications, for example, where one desires to prepare mutants employing a mutant primer strand hybridized to an underlying template, less stringent (reduced stringency) hybridization conditions will typically be needed in order to allow formation of the heteroduplex. In these circumstances, one may desire to employ salt conditions such as those of from about 0.15 M to about 0.9 M salt, at temperatures ranging from about 20°C to about 55°C. Cross-hybridizing species can thereby be readily identified as positively hybridizing signals with respect to control hybridizations. In any case, it is generally appreciated that conditions can be rendered more stringent by the addition of increasing amounts of formamide, which serves to destabilize the hybrid duplex in the same manner as increased temperature. Thus, hybridization conditions can be readily manipulated, and thus will generally be a method of choice depending on the desired results.

15 POLYNUCLEOTIDE IDENTIFICATION AND CHARACTERIZATION

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Polynucleotides may be identified, prepared and/or manipulated using any of a variety of well established techniques. For example, a polynucleotide may be identified, as described in more detail below, by screening a microarray of cDNAs for tumor-associated expression (*i.e.*, expression that is at least two fold greater in a tumor than in normal tissue, as determined using a representative assay provided herein). Such screens may be performed, for example, using a Synteni microarray (Palo Alto, CA) according to the manufacturer's instructions (and essentially as described by Schena *et al.*, *Proc. Natl. Acad. Sci. USA 93*:10614-10619, 1996 and Heller *et al.*, *Proc. Natl. Acad. Sci. USA 94*:2150-2155, 1997). Alternatively, polynucleotides may be amplified from cDNA prepared from cells expressing the proteins described herein, such as lung tumor cells. Such polynucleotides may be amplified via polymerase chain reaction (PCR). For this approach, sequence-specific primers may be designed based on the sequences provided herein, and may be purchased or synthesized.

An amplified portion of a polynucleotide of the present invention may be used to isolate a full length gene from a suitable library (e.g., a lung tumor cDNA

library) using well known techniques. Within such techniques, a library (cDNA or genomic) is screened using one or more polynucleotide probes or primers suitable for amplification. Preferably, a library is size-selected to include larger molecules. Random primed libraries may also be preferred for identifying 5' and upstream regions of genes. Genomic libraries are preferred for obtaining introns and extending 5' sequences.

For hybridization techniques, a partial sequence may be labeled (e.g., by nick-translation or end-labeling with ³²P) using well known techniques. A bacterial or bacteriophage library is then generally screened by hybridizing filters containing denatured bacterial colonies (or lawns containing phage plaques) with the labeled probe (see Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989). Hybridizing colonies or plaques are selected and expanded, and the DNA is isolated for further analysis. cDNA clones may be analyzed to determine the amount of additional sequence by, for example, PCR using a primer from the partial sequence and a primer from the vector. Restriction maps and partial sequences may be generated to identify one or more overlapping clones. The complete sequence may then be determined using standard techniques, which may involve generating a series of deletion clones. The resulting overlapping sequences can then assembled into a single contiguous sequence. A full length cDNA molecule can be generated by ligating suitable fragments, using well known techniques.

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Alternatively, there are numerous amplification techniques for obtaining a full length coding sequence from a partial cDNA sequence. Within such techniques, amplification is generally performed via PCR. Any of a variety of commercially available kits may be used to perform the amplification step. Primers may be designed using, for example, software well known in the art. Primers are preferably 22-30 nucleotides in length, have a GC content of at least 50% and anneal to the target sequence at temperatures of about 68°C to 72°C. The amplified region may be sequenced as described above, and overlapping sequences assembled into a contiguous sequence.

One such amplification technique is inverse PCR (see Triglia et al., Nucl. Acids Res. 16:8186, 1988), which uses restriction enzymes to generate a fragment

in the known region of the gene. The fragment is then circularized by intramolecular ligation and used as a template for PCR with divergent primers derived from the known region. Within an alternative approach, sequences adjacent to a partial sequence may be retrieved by amplification with a primer to a linker sequence and a primer specific to a known region. The amplified sequences are typically subjected to a second round of amplification with the same linker primer and a second primer specific to the known A variation on this procedure, which employs two primers that initiate extension in opposite directions from the known sequence, is described in WO 96/38591. Another such technique is known as "rapid amplification of cDNA ends" or RACE. This technique involves the use of an internal primer and an external primer. which hybridizes to a polyA region or vector sequence, to identify sequences that are 5' and 3' of a known sequence. Additional techniques include capture PCR (Lagerstrom et al., PCR Methods Applic. 1:111-19, 1991) and walking PCR (Parker et al., Nucl. Acids. Res. 19:3055-60, 1991). Other methods employing amplification may also be employed to obtain a full length cDNA sequence.

In certain instances, it is possible to obtain a full length cDNA sequence by analysis of sequences provided in an expressed sequence tag (EST) database, such as that available from GenBank. Searches for overlapping ESTs may generally be performed using well known programs (e.g., NCBI BLAST searches), and such ESTs may be used to generate a contiguous full length sequence. Full length DNA sequences may also be obtained by analysis of genomic fragments.

POLYNUCLEOTIDE EXPRESSION IN HOST CELLS

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In other embodiments of the invention, polynucleotide sequences or fragments thereof which encode polypeptides of the invention, or fusion proteins or functional equivalents thereof, may be used in recombinant DNA molecules to direct expression of a polypeptide in appropriate host cells. Due to the inherent degeneracy of the genetic code, other DNA sequences that encode substantially the same or a functionally equivalent amino acid sequence may be produced and these sequences may be used to clone and express a given polypeptide.

As will be understood by those of skill in the art, it may be advantageous in some instances to produce polypeptide-encoding nucleotide sequences possessing non-naturally occurring codons. For example, codons preferred by a particular prokaryotic or eukaryotic host can be selected to increase the rate of protein expression or to produce a recombinant RNA transcript having desirable properties, such as a half-life which is longer than that of a transcript generated from the naturally occurring sequence.

Moreover, the polynucleotide sequences of the present invention can be engineered using methods generally known in the art in order to alter polypeptide encoding sequences for a variety of reasons, including but not limited to, alterations which modify the cloning, processing, and/or expression of the gene product. For example, DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide sequences. In addition, site-directed mutagenesis may be used to insert new restriction sites, alter glycosylation patterns, change codon preference, produce splice variants, or introduce mutations, and so forth.

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In another embodiment of the invention, natural, modified, or recombinant nucleic acid sequences may be ligated to a heterologous sequence to encode a fusion protein. For example, to screen peptide libraries for inhibitors of polypeptide activity, it may be useful to encode a chimeric protein that can be recognized by a commercially available antibody. A fusion protein may also be engineered to contain a cleavage site located between the polypeptide-encoding sequence and the heterologous protein sequence, so that the polypeptide may be cleaved and purified away from the heterologous moiety.

Sequences encoding a desired polypeptide may be synthesized, in whole or in part, using chemical methods well known in the art (see Caruthers, M. H. et al. (1980) Nucl. Acids Res. Symp. Ser. 215-223, Horn, T. et al. (1980) Nucl. Acids Res. Symp. Ser. 225-232). Alternatively, the protein itself may be produced using chemical methods to synthesize the amino acid sequence of a polypeptide, or a portion thereof. For example, peptide synthesis can be performed using various solid-phase techniques (Roberge, J. Y. et al. (1995) Science 269:202-204) and automated synthesis may be

achieved, for example, using the ABI 431A Peptide Synthesizer (Perkin Elmer, Palo Alto, CA).

A newly synthesized peptide may be substantially purified by preparative high performance liquid chromatography (e.g., Creighton, T. (1983) Proteins, Structures and Molecular Principles, WH Freeman and Co., New York, N.Y.) or other comparable techniques available in the art. The composition of the synthetic peptides may be confirmed by amino acid analysis or sequencing (e.g., the Edman degradation procedure). Additionally, the amino acid sequence of a polypeptide, or any part thereof, may be altered during direct synthesis and/or combined using chemical methods with sequences from other proteins, or any part thereof, to produce a variant polypeptide.

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In order to express a desired polypeptide, the nucleotide sequences encoding the polypeptide, or functional equivalents, may be inserted into appropriate expression vector, *i.e.*, a vector which contains the necessary elements for the transcription and translation of the inserted coding sequence. Methods which are well known to those skilled in the art may be used to construct expression vectors containing sequences encoding a polypeptide of interest and appropriate transcriptional and translational control elements. These methods include in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. Such techniques are described in Sambrook, J. et al. (1989) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Press, Plainview, N.Y., and Ausubel, F. M. et al. (1989) Current Protocols in Molecular Biology, John Wiley & Sons, New York, N.Y.

A variety of expression vector/host systems may be utilized to contain and express polynucleotide sequences. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with virus expression vectors (e.g., baculovirus); plant cell systems transformed with virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or with bacterial expression vectors (e.g., Ti or pBR322 plasmids); or animal cell systems.

The "control elements" or "regulatory sequences" present in an expression vector are those non-translated regions of the vector--enhancers, promoters, 5' and 3' untranslated regions--which interact with host cellular proteins to carry out transcription and translation. Such elements may vary in their strength and specificity. Depending on the vector system and host utilized, any number of suitable transcription and translation elements, including constitutive and inducible promoters, may be used. For example, when cloning in bacterial systems, inducible promoters such as the hybrid lacZ promoter of the PBLUESCRIPT phagemid (Stratagene, La Jolla, Calif.) or PSPORT1 plasmid (Gibco BRL, Gaithersburg, MD) and the like may be used. In mammalian cell systems, promoters from mammalian genes or from mammalian viruses are generally preferred. If it is necessary to generate a cell line that contains multiple copies of the sequence encoding a polypeptide, vectors based on SV40 or EBV may be advantageously used with an appropriate selectable marker.

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In bacterial systems, a number of expression vectors may be selected depending upon the use intended for the expressed polypeptide. For example, when large quantities are needed, for example for the induction of antibodies, vectors which direct high level expression of fusion proteins that are readily purified may be used. Such vectors include, but are not limited to, the multifunctional E. coli cloning and expression vectors such as BLUESCRIPT (Stratagene), in which the sequence encoding the polypeptide of interest may be ligated into the vector in frame with sequences for the amino-terminal Met and the subsequent 7 residues of .beta.-galactosidase so that a hybrid protein is produced; pIN vectors (Van Heeke, G. and S. M. Schuster (1989) J. Biol. Chem. 264:5503-5509); and the like. pGEX Vectors (Promega, Madison, Wis.) may also be used to express foreign polypeptides as fusion proteins with glutathione Stransferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption to glutathione-agarose beads followed by elution in the presence of free glutathione. Proteins made in such systems may be designed to include heparin, thrombin, or factor XA protease cleavage sites so that the cloned polypeptide of interest can be released from the GST moiety at will.

In the yeast, Saccharomyces cerevisiae, a number of vectors containing constitutive or inducible promoters such as alpha factor, alcohol oxidase, and PGH may

be used. For reviews, see Ausubel et al. (supra) and Grant et al. (1987) Methods Enzymol. 153:516-544.

In cases where plant expression vectors are used, the expression of sequences encoding polypeptides may be driven by any of a number of promoters. For example, viral promoters such as the 35S and 19S promoters of CaMV may be used alone or in combination with the omega leader sequence from TMV (Takamatsu, N. (1987) EMBO J. 6:307-311. Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters may be used (Coruzzi, G. et al. (1984) EMBO J. 3:1671-1680; Broglie, R. et al. (1984) Science 224:838-843; and Winter, J. et al. (1991) Results Probl. Cell Differ. 17:85-105). These constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated transfection. Such techniques are described in a number of generally available reviews (see, for example, Hobbs, S. or Murry, L. E. in McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York, N.Y.; pp. 191-196).

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An insect system may also be used to express a polypeptide of interest. For example, in one such system, Autographa californica nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes in Spodoptera frugiperda cells or in Trichoplusia larvae. The sequences encoding the polypeptide may be cloned into a non-essential region of the virus, such as the polyhedrin gene, and placed under control of the polyhedrin promoter. Successful insertion of the polypeptide-encoding sequence will render the polyhedrin gene inactive and produce recombinant virus lacking coat protein. The recombinant viruses may then be used to infect, for example, S. frugiperda cells or Trichoplusia larvae in which the polypeptide of interest may be expressed (Engelhard, E. K. et al. (1994) Proc. Natl. Acad. Sci. 91:3224-3227).

In mammalian host cells, a number of viral-based expression systems are generally available. For example, in cases where an adenovirus is used as an expression vector, sequences encoding a polypeptide of interest may be ligated into an adenovirus transcription/translation complex consisting of the late promoter and tripartite leader sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain a viable virus which is capable of expressing the polypeptide in infected host cells (Logan, J. and Shenk, T. (1984) *Proc. Natl. Acad. Sci. 81*:3655-3659). In addition,

transcription enhancers, such as the Rous sarcoma virus (RSV) enhancer, may be used to increase expression in mammalian host cells.

Specific initiation signals may also be used to achieve more efficient translation of sequences encoding a polypeptide of interest. Such signals include the ATG initiation codon and adjacent sequences. In cases where sequences encoding the polypeptide, its initiation codon, and upstream sequences are inserted into the appropriate expression vector, no additional transcriptional or translational control signals may be needed. However, in cases where only coding sequence, or a portion thereof, is inserted, exogenous translational control signals including the ATG initiation codon should be provided. Furthermore, the initiation codon should be in the correct reading frame to ensure translation of the entire insert. Exogenous translational elements and initiation codons may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers which are appropriate for the particular cell system which is used, such as those described in the literature (Scharf, D. et al. (1994) Results Probl. Cell Differ. 20:125-162).

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In addition, a host cell strain may be chosen for its ability to modulate the expression of the inserted sequences or to process the expressed protein in the desired fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation. glycosylation, phosphorylation, lipidation, and acylation. Post-translational processing which cleaves a "prepro" form of the protein may also be used to facilitate correct insertion, folding and/or function. Different host cells such as CHO, HeLa, MDCK, HEK293, and WI38, which have specific cellular machinery and characteristic mechanisms for such post-translational activities, may be chosen to ensure the correct modification and processing of the foreign protein.

For long-term, high-yield production of recombinant proteins, stable expression is generally preferred. For example, cell lines which stably express a polynucleotide of interest may be transformed using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. Following the introduction of the vector, cells may be allowed to grow for 1-2 days in an enriched media before they are switched to selective media. The purpose of the selectable marker is to confer

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resistance to selection, and its presence allows growth and recovery of cells which successfully express the introduced sequences. Resistant clones of stably transformed cells may be proliferated using tissue culture techniques appropriate to the cell type.

Any number of selection systems may be used to recover transformed cell lines. These include, but are not limited to, the herpes simplex virus thymidine kinase (Wigler, M. et al. (1977) Cell 11:223-32) and adenine phosphoribosyltransferase (Lowy, I. et al. (1990) Cell 22:817-23) genes which can be employed in tk.sup.- or aprt.sup.- cells, respectively. Also, antimetabolite, antibiotic or herbicide resistance can be used as the basis for selection; for example, dhfr which confers resistance to methotrexate (Wigler, M. et al. (1980) Proc. Natl. Acad. Sci. 77:3567-70); npt, which confers resistance to the aminoglycosides, neomycin and G-418 (Colbere-Garapin, F. et al (1981) J. Mol. Biol. 150:1-14); and als or pat, which confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively (Murry, supra). Additional selectable genes have been described, for example, trpB, which allows cells to utilize indole in place of tryptophan, or hisD, which allows cells to utilize histinol in place of histidine (Hartman, S. C. and R. C. Mulligan (1988) Proc. Natl. Acad. Sci. 85:8047-51). Recently, the use of visible markers has gained popularity with such markers as anthocyanins, beta-glucuronidase and its substrate GUS, and luciferase and its substrate luciferin, being widely used not only to identify transformants, but also to quantify the amount of transient or stable protein expression attributable to a specific vector system (Rhodes, C. A. et al. (1995) Methods Mol. Biol. 55:121-131).

Although the presence/absence of marker gene expression suggests that the gene of interest is also present, its presence and expression may need to be confirmed. For example, if the sequence encoding a polypeptide is inserted within a marker gene sequence, recombinant cells containing sequences can be identified by the absence of marker gene function. Alternatively, a marker gene can be placed in tandem with a polypeptide-encoding sequence under the control of a single promoter. Expression of the marker gene in response to induction or selection usually indicates expression of the tandem gene as well.

Alternatively, host cells which contain and express a desired polynucleotide sequence may be identified by a variety of procedures known to those of

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skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations and protein bioassay or immunoassay techniques which include membrane, solution, or chip based technologies for the detection and/or quantification of nucleic acid or protein.

A variety of protocols for detecting and measuring the expression of polynucleotide-encoded products, using either polyclonal or monoclonal antibodies specific for the product are known in the art. Examples include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), and fluorescence activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering epitopes on a given polypeptide may be preferred for some applications, but a competitive binding assay may also be employed. These and other assays are described, among other places, in Hampton, R. et al. (1990; Serological Methods, a Laboratory Manual, APS Press, St Paul. Minn.) and Maddox, D. E. et al. (1983; J. Exp. Med. 158:1211-1216).

A wide variety of labels and conjugation techniques are known by those skilled in the art and may be used in various nucleic acid and amino acid assays. Means for producing labeled hybridization or PCR probes for detecting sequences related to polynucleotides include oligolabeling, nick translation, end-labeling or PCR amplification using a labeled nucleotide. Alternatively, the sequences, or any portions thereof may be cloned into a vector for the production of an mRNA probe. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by addition of an appropriate RNA polymerase such as T7, T3, or SP6 and labeled nucleotides. These procedures may be conducted using a variety of commercially available kits. Suitable reporter molecules or labels, which may be used include radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

Host cells transformed with a polynucleotide sequence of interest may be cultured under conditions suitable for the expression and recovery of the protein from cell culture. The protein produced by a recombinant cell may be secreted or contained intracellularly depending on the sequence and/or the vector used. As will be understood by those of skill in the art, expression vectors containing polynucleotides of the

invention may be designed to contain signal sequences which direct secretion of the encoded polypeptide through a prokaryotic or eukaryotic cell membrane. Other recombinant constructions may be used to join sequences encoding a polypeptide of interest to nucleotide sequence encoding a polypeptide domain which will facilitate purification of soluble proteins. Such purification facilitating domains include, but are not limited to, metal chelating peptides such as histidine-tryptophan modules that allow purification on immobilized metals, protein A domains that allow purification on immobilized immunoglobulin, and the domain utilized in the FLAGS extension/affinity purification system (Immunex Corp., Seattle, Wash.). The inclusion of cleavable linker sequences such as those specific for Factor XA or enterokinase (Invitrogen. San Diego, Calif.) between the purification domain and the encoded polypeptide may be used to facilitate purification. One such expression vector provides for expression of a fusion protein containing a polypeptide of interest and a nucleic acid encoding 6 histidine residues preceding a thioredoxin or an enterokinase cleavage site. The histidine residues facilitate purification on IMIAC (immobilized metal ion affinity chromatography) as described in Porath, J. et al. (1992, Prot. Exp. Purif. 3:263-281) while the enterokinase cleavage site provides a means for purifying the desired polypeptide from the fusion protein. A discussion of vectors which contain fusion proteins is provided in Kroll, D. J. et al. (1993; DNA Cell Biol. 12:441-453).

In addition to recombinant production methods, polypeptides of the invention, and fragments thereof, may be produced by direct peptide synthesis using solid-phase techniques (Merrifield J. (1963) *J. Am. Chem. Soc.* 85:2149-2154). Protein synthesis may be performed using manual techniques or by automation. Automated synthesis may be achieved, for example, using Applied Biosystems 431A Peptide Synthesizer (Perkin Elmer). Alternatively, various fragments may be chemically synthesized separately and combined using chemical methods to produce the full length molecule.

SITE-SPÉCIFIC MUTAGENESIS

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Site-specific mutagenesis is a technique useful in the preparation of individual peptides, or biologically functional equivalent polypeptides, through specific

mutagenesis of the underlying polynucleotides that encode them. The technique, well-known to those of skill in the art, further provides a ready ability to prepare and test sequence variants, for example, incorporating one or more of the foregoing considerations, by introducing one or more nucleotide sequence changes into the DNA. Site-specific mutagenesis allows the production of mutants through the use of specific oligonucleotide sequences which encode the DNA sequence of the desired mutation, as well as a sufficient number of adjacent nucleotides, to provide a primer sequence of sufficient size and sequence complexity to form a stable duplex on both sides of the deletion junction being traversed. Mutations may be employed in a selected polynucleotide sequence to improve, alter, decrease, modify, or otherwise change the properties of the polynucleotide itself, and/or alter the properties, activity, composition, stability, or primary sequence of the encoded polypeptide.

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In certain embodiments of the present invention, the inventors contemplate the mutagenesis of the disclosed polynucleotide sequences to alter one or more properties of the encoded polypeptide, such as the antigenicity of a polypeptide vaccine. The techniques of site-specific mutagenesis are well-known in the art, and are widely used to create variants of both polypeptides and polynucleotides. For example, site-specific mutagenesis is often used to alter a specific portion of a DNA molecule. In such embodiments, a primer comprising typically about 14 to about 25 nucleotides or so in length is employed, with about 5 to about 10 residues on both sides of the junction of the sequence being altered.

As will be appreciated by those of skill in the art, site-specific mutagenesis techniques have often employed a phage vector that exists in both a single stranded and double stranded form. Typical vectors useful in site-directed mutagenesis include vectors such as the M13 phage. These phage are readily commercially-available and their use is generally well-known to those skilled in the art. Double-stranded plasmids are also routinely employed in site directed mutagenesis that eliminates the step of transferring the gene of interest from a plasmid to a phage.

In general, site-directed mutagenesis in accordance herewith is performed by first obtaining a single-stranded vector or melting apart of two strands of a double-stranded vector that includes within its sequence a DNA sequence that

encodes the desired peptide. An oligonucleotide primer bearing the desired mutated sequence is prepared, generally synthetically. This primer is then annealed with the single-stranded vector, and subjected to DNA polymerizing enzymes such as *E. coli* polymerase I Klenow fragment, in order to complete the synthesis of the mutation-bearing strand. Thus, a heteroduplex is formed wherein one strand encodes the original non-mutated sequence and the second strand bears the desired mutation. This heteroduplex vector is then used to transform appropriate cells, such as *E. coli* cells, and clones are selected which include recombinant vectors bearing the mutated sequence arrangement.

The preparation of sequence variants of the selected peptide-encoding DNA segments using site-directed mutagenesis provides a means of producing potentially useful species and is not meant to be limiting as there are other ways in which sequence variants of peptides and the DNA sequences encoding them may be obtained. For example, recombinant vectors encoding the desired peptide sequence may be treated with mutagenic agents, such as hydroxylamine, to obtain sequence variants. Specific details regarding these methods and protocols are found in the teachings of Maloy et al., 1994; Segal, 1976; Prokop and Bajpai, 1991; Kuby, 1994; and Maniatis et al., 1982, each incorporated herein by reference, for that purpose.

As used herein, the term "oligonucleotide directed mutagenesis procedure" refers to template-dependent processes and vector-mediated propagation which result in an increase in the concentration of a specific nucleic acid molecule relative to its initial concentration, or in an increase in the concentration of a detectable signal, such as amplification. As used herein, the term "oligonucleotide directed mutagenesis procedure" is intended to refer to a process that involves the template-dependent extension of a primer molecule. The term template dependent process refers to nucleic acid synthesis of an RNA or a DNA molecule wherein the sequence of the newly synthesized strand of nucleic acid is dictated by the well-known rules of complementary base pairing (see, for example, Watson, 1987). Typically, vector mediated methodologies involve the introduction of the nucleic acid fragment into a DNA or RNA vector, the clonal amplification of the vector, and the recovery of

the amplified nucleic acid fragment. Examples of such methodologies are provided by U. S. Patent No. 4,237,224, specifically incorporated herein by reference in its entirety.

POLYNUCLEOTIDE AMPLIFICATION TECHNIQUES

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A number of template dependent processes are available to amplify the target sequences of interest present in a sample. One of the best known amplification methods is the polymerase chain reaction (PCRTM) which is described in detail in U.S. Patent Nos. 4,683,195, 4,683,202 and 4,800,159, each of which is incorporated herein by reference in its entirety. Briefly, in PCRTM, two primer sequences are prepared which are complementary to regions on opposite complementary strands of the target sequence. An excess of deoxynucleoside triphosphates is added to a reaction mixture along with a DNA polymerase (e.g., Tag polymerase). If the target sequence is present in a sample, the primers will bind to the target and the polymerase will cause the primers to be extended along the target sequence by adding on nucleotides. By raising and lowering the temperature of the reaction mixture, the extended primers will dissociate from the target to form reaction products, excess primers will bind to the target and to the reaction product and the process is repeated. Preferably reverse transcription and PCRTM amplification procedure may be performed in order to quantify the amount of mRNA amplified. Polymerase chain reaction methodologies are well known in the art.

Another method for amplification is the ligase chain reaction (referred to as LCR), disclosed in Eur. Pat. Appl. Publ. No. 320,308 (specifically incorporated herein by reference in its entirety). In LCR, two complementary probe pairs are prepared, and in the presence of the target sequence, each pair will bind to opposite complementary strands of the target such that they abut. In the presence of a ligase, the two probe pairs will link to form a single unit. By temperature cycling, as in PCRTM, bound ligated units dissociate from the target and then serve as "target sequences" for ligation of excess probe pairs. U.S. Patent No. 4,883,750, incorporated herein by reference in its entirety, describes an alternative method of amplification similar to LCR for binding probe pairs to a target sequence.

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Qbeta Replicase, described in PCT Intl. Pat. Appl. Publ. No. PCT/US87/00880, incorporated herein by reference in its entirety, may also be used as still another amplification method in the present invention. In this method, a replicative sequence of RNA that has a region complementary to that of a target is added to a sample in the presence of an RNA polymerase. The polymerase will copy the replicative sequence that can then be detected.

An isothermal amplification method, in which restriction endonucleases and ligases are used to achieve the amplification of target molecules that contain nucleotide 5'- $[\alpha$ -thio]triphosphates in one strand of a restriction site (Walker *et al.*, 1992, incorporated herein by reference in its entirety), may also be useful in the amplification of nucleic acids in the present invention.

Strand Displacement Amplification (SDA) is another method of carrying out isothermal amplification of nucleic acids which involves multiple rounds of strand displacement and synthesis, *i.e.* nick translation. A similar method, called Repair Chain Reaction (RCR) is another method of amplification which may be useful in the present invention and is involves annealing several probes throughout a region targeted for amplification, followed by a repair reaction in which only two of the four bases are present. The other two bases can be added as biotinylated derivatives for easy detection. A similar approach is used in SDA.

Sequences can also be detected using a cyclic probe reaction (CPR). In CPR, a probe having a 3' and 5' sequences of non-target DNA and an internal or "middle" sequence of the target protein specific RNA is hybridized to DNA which is present in a sample. Upon hybridization, the reaction is treated with RNaseH, and the products of the probe are identified as distinctive products by generating a signal that is released after digestion. The original template is annealed to another cycling probe and the reaction is repeated. Thus, CPR involves amplifying a signal generated by hybridization of a probe to a target gene specific expressed nucleic acid.

Still other amplification methods described in Great Britain Pat. Appl. No. 2 202 328, and in PCT Intl. Pat. Appl. Publ. No. PCT/US89/01025, each of which is incorporated herein by reference in its entirety, may be used in accordance with the present invention. In the former application, "modified" primers are used in a PCR-

like, template and enzyme dependent synthesis. The primers may be modified by labeling with a capture moiety (e.g., biotin) and/or a detector moiety (e.g., enzyme). In the latter application, an excess of labeled probes is added to a sample. In the presence of the target sequence, the probe binds and is cleaved catalytically. After cleavage, the target sequence is released intact to be bound by excess probe. Cleavage of the labeled probe signals the presence of the target sequence.

Other nucleic acid amplification procedures include transcription-based amplification systems (TAS) (Kwoh et al., 1989; PCT Intl. Pat. Appl. Publ. No. WO 88/10315, incorporated herein by reference in its entirety), including nucleic acid sequence based amplification (NASBA) and 3SR. In NASBA, the nucleic acids can be prepared for amplification by standard phenol/chloroform extraction, heat denaturation of a sample, treatment with lysis buffer and minispin columns for isolation of DNA and RNA or guanidinium chloride extraction of RNA. These amplification techniques involve annealing a primer that has sequences specific to the target sequence. Following polymerization, DNA/RNA hybrids are digested with RNase H while double stranded DNA molecules are heat-denatured again. In either case the single stranded DNA is made fully double stranded by addition of second target-specific primer, followed by polymerization. The double stranded DNA molecules are then multiply transcribed by a polymerase such as T7 or SP6. In an isothermal cyclic reaction, the RNAs are reverse transcribed into DNA, and transcribed once again with a polymerase such as T7 or SP6. The resulting products, whether truncated or complete, indicate target-specific sequences.

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Eur. Pat. Appl. Publ. No. 329,822, incorporated herein by reference in its entirety, disclose a nucleic acid amplification process involving cyclically synthesizing single-stranded RNA ("ssRNA"), ssDNA, and double-stranded DNA (dsDNA), which may be used in accordance with the present invention. The ssRNA is a first template for a first primer oligonucleotide, which is elongated by reverse transcriptase (RNA-dependent DNA polymerase). The RNA is then removed from resulting DNA:RNA duplex by the action of ribonuclease H (RNase H, an RNase specific for RNA in a duplex with either DNA or RNA). The resultant ssDNA is a second template for a second primer, which also includes the sequences of an RNA polymerase

promoter (exemplified by T7 RNA polymerase) 5' to its homology to its template. This primer is then extended by DNA polymerase (exemplified by the large "Klenow" fragment of *E. coli* DNA polymerase I), resulting as a double-stranded DNA ("dsDNA") molecule, having a sequence identical to that of the original RNA between the primers and having additionally, at one end, a promoter sequence. This promoter sequence can be used by the appropriate RNA polymerase to make many RNA copies of the DNA. These copies can then re-enter the cycle leading to very swift amplification. With proper choice of enzymes, this amplification can be done isothermally without addition of enzymes at each cycle. Because of the cyclical nature of this process, the starting sequence can be chosen to be in the form of either DNA or RNA.

PCT Intl. Pat. Appl. Publ. No. WO 89/06700, incorporated herein by reference in its entirety, disclose a nucleic acid sequence amplification scheme based on the hybridization of a promoter/primer sequence to a target single-stranded DNA ("ssDNA") followed by transcription of many RNA copies of the sequence. This scheme is not cyclic; *i.e.* new templates are not produced from the resultant RNA transcripts. Other amplification methods include "RACE" (Frohman, 1990), and "one-sided PCR" (Ohara, 1989) which are well-known to those of skill in the art.

Methods based on ligation of two (or more) oligonucleotides in the presence of nucleic acid having the sequence of the resulting "di-oligonucleotide", thereby amplifying the di-oligonucleotide (Wu and Dean, 1996, incorporated herein by reference in its entirety), may also be used in the amplification of DNA sequences of the present invention.

BIOLOGICAL FUNCTIONAL EQUIVALENTS

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Modification and changes may be made in the structure of the polynucleotides and polypeptides of the present invention and still obtain a functional molecule that encodes a polypeptide with desirable characteristics. As mentioned above, it is often desirable to introduce one or more mutations into a specific polynucleotide sequence. In certain circumstances, the resulting encoded polypeptide

sequence is altered by this mutation, or in other cases, the sequence of the polypeptide is unchanged by one or more mutations in the encoding polynucleotide.

When it is desirable to alter the amino acid sequence of a polypeptide to create an equivalent, or even an improved, second-generation molecule, the amino acid changes may be achieved by changing one or more of the codons of the encoding DNA sequence, according to Table 1.

For example, certain amino acids may be substituted for other amino acids in a protein structure without appreciable loss of interactive binding capacity with structures such as, for example, antigen-binding regions of antibodies or binding sites on substrate molecules. Since it is the interactive capacity and nature of a protein that defines that protein's biological functional activity, certain amino acid sequence substitutions can be made in a protein sequence, and, of course, its underlying DNA coding sequence, and nevertheless obtain a protein with like properties. It is thus contemplated by the inventors that various changes may be made in the peptide sequences of the disclosed compositions, or corresponding DNA sequences which encode said peptides without appreciable loss of their biological utility or activity.

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TABLE 1

Amino Acids			Codons					
Alanine	Ala	A	GCA	GCC	GCG	GCU		
Cysteine	Cys	C	UGC	UGU				
Aspartic acid	Asp	D	GAC	GAU				
Glutamic acid	Glu	E	GAA	GAG				
Phenylalanine	Phe	F	UUC	UUU				
Glycine	Gly	G	GGA	GGC	GGG	GGU		
Histidine	His	Н	CAC	CAU				
Isoleucine	Ile	I	AUA	AUC	AUU			
Lysine	Lys	K	AAA	AAG				•
Leucine	Leu	L	UUA	UUG	CUA	CUC	CUG	CUU
Methionine	Met	M	AUG					
Asparagine	Asn	N	AAC	AAU				
Proline	Pro	P	CCA	CCC	CCG	CCU		
Glutamine	Gin	Q	CAA	CAG				
Arginine	Arg	R	AGA	AGG	CGA	CGC	CGG	CGU
Serine	Ser	S	AGC	AGU	UCA	UCC	UCG	UCU
Threonine	Thr	T	ACA	ACC	ACG	ACU		
Valine	Val	V	GUA	GUC	GUG	GUU		
Tryptophan	Trp	w	UGG					
Tyrosine	Tyr.	Y	UAC	UAU				

In making such changes, the hydropathic index of amino acids may be considered. The importance of the hydropathic amino acid index in conferring interactive biologic function on a protein is generally understood in the art (Kyte and Doolittle, 1982, incorporated herein by reference). It is accepted that the relative hydropathic character of the amino acid contributes to the secondary structure of the resultant protein, which in turn defines the interaction of the protein with other molecules, for example, enzymes, substrates, receptors, DNA, antibodies, antigens, and the like. Each amino acid has been assigned a hydropathic index on the basis of its hydrophobicity and charge characteristics (Kyte and Doolittle, 1982). These values are:

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isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine (+2.5); methionine (+1.9); alanine (+1.8); glycine (-0.4); threonine (-0.7); serine (-0.8); tryptophan (-0.9); tyrosine (-1.3); proline (-1.6); histidine (-3.2); glutamate (-3.5); glutamine (-3.5); asparagine (-3.5); lysine (-3.9); and arginine (-4.5).

It is known in the art that certain amino acids may be substituted by other amino acids having a similar hydropathic index or score and still result in a protein with similar biological activity, *i.e.* still obtain a biological functionally equivalent protein. In making such changes, the substitution of amino acids whose hydropathic indices are within ± 2 is preferred, those within ± 1 are particularly preferred, and those within ± 0.5 are even more particularly preferred. It is also understood in the art that the substitution of like amino acids can be made effectively on the basis of hydrophilicity. U. S. Patent 4,554,101 (specifically incorporated herein by reference in its entirety), states that the greatest local average hydrophilicity of a protein, as governed by the hydrophilicity of its adjacent amino acids, correlates with a biological property of the protein.

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As detailed in U. S. Patent 4,554,101, the following hydrophilicity values have been assigned to amino acid residues: arginine (± 3.0) ; lysine (± 3.0) ; aspartate $(\pm 3.0 \pm 1)$; glutamate $(\pm 3.0 \pm 1)$; serine (± 0.3) ; asparagine (± 0.2) ; glutamine (± 0.2) ; glycine (± 0.2) ; glycine (± 0.4) ; proline (± 0.5) ; alanine (± 0.5) ; histidine (± 0.5) ; cysteine (± 0.10) ; methionine (± 0.10) ; valine (± 0.10) ; leucine (± 0.10) ; isoleucine (± 0.10) ; tyrosine (± 0.10) ; phenylalanine (± 0.10) ; tryptophan (± 0.10) . It is understood that an amino acid can be substituted for another having a similar hydrophilicity value and still obtain a biologically equivalent, and in particular, an immunologically equivalent protein. In such changes, the substitution of amino acids whose hydrophilicity values are within ± 0.10 is preferred, those within ± 0.10 are even more particularly preferred.

As outlined above, amino acid substitutions are generally therefore based on the relative similarity of the amino acid side-chain substituents, for example, their hydrophobicity, hydrophilicity, charge, size, and the like. Exemplary substitutions that take various of the foregoing characteristics into consideration are well known to those

of skill in the art and include: arginine and lysine; glutamate and aspartate; serine and threonine; glutamine and asparagine; and valine, leucine and isoleucine.

In addition, any polynucleotide may be further modified to increase stability in vivo. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends; the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages in the backbone; and/or the inclusion of nontraditional bases such as inosine, queosine and wybutosine, as well as acetylmethyl-, thio- and other modified forms of adenine, cytidine, guanine, thymine and uridine.

10 In vivo Polynucleotide Delivery Techniques

In additional embodiments, genetic constructs comprising one or more of the polynucleotides of the invention are introduced into cells *in vivo*. This may be achieved using any of a variety or well known approaches, several of which are outlined below for the purpose of illustration.

15 1. ADENOVIRUS

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One of the preferred methods for *in vivo* delivery of one or more nucleic acid sequences involves the use of an adenovirus expression vector. "Adenovirus expression vector" is meant to include those constructs containing adenovirus sequences sufficient to (a) support packaging of the construct and (b) to express a polynucleotide that has been cloned therein in a sense or antisense orientation. Of course, in the context of an antisense construct, expression does not require that the gene product be synthesized.

The expression vector comprises a genetically engineered form of an adenovirus. Knowledge of the genetic organization of adenovirus, a 36 kb, linear, double-stranded DNA virus, allows substitution of large pieces of adenoviral DNA with foreign sequences up to 7 kb (Grunhaus and Horwitz, 1992). In contrast to retrovirus, the adenoviral infection of host cells does not result in chromosomal integration because adenoviral DNA can replicate in an episomal manner without potential genotoxicity. Also, adenoviruses are structurally stable, and no genome rearrangement

has been detected after extensive amplification. Adenovirus can infect virtually all epithelial cells regardless of their cell cycle stage. So far, adenoviral infection appears to be linked only to mild disease such as acute respiratory disease in humans.

Adenovirus is particularly suitable for use as a gene transfer vector because of its mid-sized genome, ease of manipulation, high titer, wide target-cell range and high infectivity. Both ends of the viral genome contain 100-200 base pair inverted repeats (ITRs), which are cis elements necessary for viral DNA replication and The early (E) and late (L) regions of the genome contain different packaging. transcription units that are divided by the onset of viral DNA replication. The E1 region (E1A and E1B) encodes proteins responsible for the regulation of transcription of the viral genome and a few cellular genes. The expression of the E2 region (E2A and E2B) results in the synthesis of the proteins for viral DNA replication. These proteins are involved in DNA replication, late gene expression and host cell shut-off (Renan, 1990). The products of the late genes, including the majority of the viral capsid proteins, are expressed only after significant processing of a single primary transcript issued by the major late promoter (MLP). The MLP, (located at 16.8 m.u.) is particularly efficient during the late phase of infection, and all the mRNA's issued from this promoter possess a 5'-tripartite leader (TPL) sequence which makes them preferred mRNA's for translation.

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In a current system, recombinant adenovirus is generated from homologous recombination between shuttle vector and provirus vector. Due to the possible recombination between two proviral vectors, wild-type adenovirus may be generated from this process. Therefore, it is critical to isolate a single clone of virus from an individual plaque and examine its genomic structure.

Generation and propagation of the current adenovirus vectors, which are replication deficient, depend on a unique helper cell line, designated 293, which was transformed from human embryonic kidney cells by Ad5 DNA fragments and constitutively expresses E1 proteins (Graham *et al.*, 1977). Since the E3 region is dispensable from the adenovirus genome (Jones and Shenk, 1978), the current adenovirus vectors, with the help of 293 cells, carry foreign DNA in either the E1, the D3 or both regions (Graham and Prevec, 1991). In nature, adenovirus can package

approximately 105% of the wild-type genome (Ghosh-Choudhury et al., 1987), providing capacity for about 2 extra kB of DNA. Combined with the approximately 5.5 kB of DNA that is replaceable in the E1 and E3 regions, the maximum capacity of the current adenovirus vector is under 7.5 kB, or about 15% of the total length of the vector. More than 80% of the adenovirus viral genome remains in the vector backbone and is the source of vector-borne cytotoxicity. Also, the replication deficiency of the E1-deleted virus is incomplete. For example, leakage of viral gene expression has been observed with the currently available vectors at high multiplicities of infection (MOI) (Mulligan, 1993).

Helper cell lines may be derived from human cells such as human embryonic kidney cells, muscle cells, hematopoietic cells or other human embryonic mesenchymal or epithelial cells. Alternatively, the helper cells may be derived from the cells of other mammalian species that are permissive for human adenovirus. Such cells include, e.g., Vero cells or other monkey embryonic mesenchymal or epithelial cells. As stated above, the currently preferred helper cell line is 293.

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Recently, Racher *et al.* (1995) disclosed improved methods for culturing 293 cells and propagating adenovirus. In one format, natural cell aggregates are grown by inoculating individual cells into 1 liter siliconized spinner flasks (Techne, Cambridge, UK) containing 100-200 ml of medium. Following stirring at 40 rpm, the cell viability is estimated with trypan blue. In another format, Fibra-Cel microcarriers (Bibby Sterlin, Stone, UK) (5 g/l) is employed as follows. A cell inoculum, resuspended in 5 ml of medium, is added to the carrier (50 ml) in a 250 ml Erlenmeyer flask and left stationary, with occasional agitation, for 1 to 4 h. The medium is then replaced with 50 ml of fresh medium and shaking initiated. For virus production, cells are allowed to grow to about 80% confluence, after which time the medium is replaced (to 25% of the final volume) and adenovirus added at an MOI of 0.05. Cultures are left stationary overnight, following which the volume is increased to 100% and shaking commenced for another 72 h.

Other than the requirement that the adenovirus vector be replication defective, or at least conditionally defective, the nature of the adenovirus vector is not believed to be crucial to the successful practice of the invention. The adenovirus may

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be of any of the 42 different known serotypes or subgroups A-F. Adenovirus type 5 of subgroup C is the preferred starting material in order to obtain a conditional replication-defective adenovirus vector for use in the present invention, since Adenovirus type 5 is a human adenovirus about which a great deal of biochemical and genetic information is known, and it has historically been used for most constructions employing adenovirus as a vector.

As stated above, the typical vector according to the present invention is replication defective and will not have an adenovirus E1 region. Thus, it will be most convenient to introduce the polynucleotide encoding the gene of interest at the position from which the E1-coding sequences have been removed. However, the position of insertion of the construct within the adenovirus sequences is not critical to the invention. The polynucleotide encoding the gene of interest may also be inserted in lieu of the deleted E3 region in E3 replacement vectors as described by Karlsson *et al.* (1986) or in the E4 region where a helper cell line or helper virus complements the E4 defect.

Adenovirus is easy to grow and manipulate and exhibits broad host range in vitro and in vivo. This group of viruses can be obtained in high titers, e.g., 10⁹-10¹¹ plaque-forming units per ml, and they are highly infective. The life cycle of adenovirus does not require integration into the host cell genome. The foreign genes delivered by adenovirus vectors are episomal and, therefore, have low genotoxicity to host cells. No side effects have been reported in studies of vaccination with wild-type adenovirus (Couch et al., 1963; Top et al., 1971), demonstrating their safety and therapeutic potential as in vivo gene transfer vectors.

Adenovirus vectors have been used in eukaryotic gene expression (Levrero et al., 1991; Gomez-Foix et al., 1992) and vaccine development (Grunhaus and Horwitz, 1992; Graham and Prevec, 1992). Recently, animal studies suggested that recombinant adenovirus could be used for gene therapy (Stratford-Perricaudet and Perricaudet, 1991; Stratford-Perricaudet et al., 1990; Rich et al., 1993). Studies in administering recombinant adenovirus to different tissues include trachea instillation (Rosenfeld et al., 1991; Rosenfeld et al., 1992), muscle injection (Ragot et al., 1993),

peripheral intravenous injections (Herz and Gerard, 1993) and stereotactic inoculation into the brain (Le Gal La Salle et al., 1993).

2. Retroviruses

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The retroviruses are a group of single-stranded RNA viruses characterized by an ability to convert their RNA to double-stranded DNA in infected cells by a process of reverse-transcription (Coffin, 1990). The resulting DNA then stably integrates into cellular chromosomes as a provirus and directs synthesis of viral proteins. The integration results in the retention of the viral gene sequences in the recipient cell and its descendants. The retroviral genome contains three genes, gag, pol, and env that code for capsid proteins, polymerase enzyme, and envelope components, respectively. A sequence found upstream from the gag gene contains a signal for packaging of the genome into virions. Two long terminal repeat (LTR) sequences are present at the 5' and 3' ends of the viral genome. These contain strong promoter and enhancer sequences and are also required for integration in the host cell genome (Coffin, 1990).

In order to construct a retroviral vector, a nucleic acid encoding one or more oligonucleotide or polynucleotide sequences of interest is inserted into the viral genome in the place of certain viral sequences to produce a virus that is replication-defective. In order to produce virions, a packaging cell line containing the gag, pol, and env genes but without the LTR and packaging components is constructed (Mann *et al.*, 1983). When a recombinant plasmid containing a cDNA, together with the retroviral LTR and packaging sequences is introduced into this cell line (by calcium phosphate precipitation for example), the packaging sequence allows the RNA transcript of the recombinant plasmid to be packaged into viral particles, which are then secreted into the culture media (Nicolas and Rubenstein, 1988; Temin, 1986; Mann *et al.*, 1983). The media containing the recombinant retroviruses is then collected, optionally concentrated, and used for gene transfer. Retroviral vectors are able to infect a broad variety of cell types. However, integration and stable expression require the division of host cells (Paskind *et al.*, 1975).

A novel approach designed to allow specific targeting of retrovirus vectors was recently developed based on the chemical modification of a retrovirus by the chemical addition of lactose residues to the viral envelope. This modification could permit the specific infection of hepatocytes *via* sialoglycoprotein receptors.

A different approach to targeting of recombinant retroviruses was designed in which biotinylated antibodies against a retroviral envelope protein and against a specific cell receptor were used. The antibodies were coupled *via* the biotin components by using streptavidin (Roux *et al.*, 1989). Using antibodies against major histocompatibility complex class I and class II antigens, they demonstrated the infection of a variety of human cells that bore those surface antigens with an ecotropic virus *in vitro* (Roux *et al.*, 1989).

3. ADENO-ASSOCIATED VIRUSES

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AAV (Ridgeway, 1988; Hermonat and Muzycska, 1984) is a parovirus, discovered as a contamination of adenoviral stocks. It is a ubiquitous virus (antibodies are present in 85% of the US human population) that has not been linked to any disease. It is also classified as a dependovirus, because its replications is dependent on the presence of a helper virus, such as adenovirus. Five serotypes have been isolated, of which AAV-2 is the best characterized. AAV has a single-stranded linear DNA that is encapsidated into capsid proteins VP1, VP2 and VP3 to form an icosahedral virion of 20 to 24 nm in diameter (Muzyczka and McLaughlin, 1988).

The AAV DNA is approximately 4.7 kilobases long. It contains two open reading frames and is flanked by two ITRs. There are two major genes in the AAV genome: rep and cap. The rep gene codes for proteins responsible for viral replications, whereas cap codes for capsid protein VP1-3. Each ITR forms a T-shaped hairpin structure. These terminal repeats are the only essential cis components of the AAV for chromosomal integration. Therefore, the AAV can be used as a vector with all viral coding sequences removed and replaced by the cassette of genes for delivery. Three viral promoters have been identified and named p5, p19, and p40, according to their map position. Transcription from p5 and p19 results in production of rep proteins,

and transcription from p40 produces the capsid proteins (Hermonat and Muzyczka, 1984).

There are several factors that prompted researchers to study the possibility of using rAAV as an expression vector. One is that the requirements for delivering a gene to integrate into the host chromosome are surprisingly few. It is necessary to have the 145-bp ITRs, which are only 6% of the AAV genome. This leaves room in the vector to assemble a 4.5-kb DNA insertion. While this carrying capacity may prevent the AAV from delivering large genes, it is amply suited for delivering the antisense constructs of the present invention.

AAV is also a good choice of delivery vehicles due to its safety. There is a relatively complicated rescue mechanism: not only wild type adenovirus but also AAV genes are required to mobilize rAAV. Likewise, AAV is not pathogenic and not associated with any disease. The removal of viral coding sequences minimizes immune reactions to viral gene expression, and therefore, rAAV does not evoke an inflammatory response.

4. OTHER VIRAL VECTORS AS EXPRESSION CONSTRUCTS

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Other viral vectors may be employed as expression constructs in the present invention for the delivery of oligonucleotide or polynucleotide sequences to a host cell. Vectors derived from viruses such as vaccinia virus (Ridgeway, 1988; Coupar *et al.*, 1988), lentiviruses, polio viruses and herpes viruses may be employed. They offer several attractive features for various mammalian cells (Friedmann, 1989; Ridgeway, 1988; Coupar *et al.*, 1988; Horwich *et al.*, 1990).

With the recent recognition of defective hepatitis B viruses, new insight was gained into the structure-function relationship of different viral sequences. *In vitro* studies showed that the virus could retain the ability for helper-dependent packaging and reverse transcription despite the deletion of up to 80% of its genome (Horwich *et al.*, 1990). This suggested that large portions of the genome could be replaced with foreign genetic material. The hepatotropism and persistence (integration) were particularly attractive properties for liver-directed gene transfer. Chang *et al.* (1991) introduced the chloramphenicol acetyltransferase (CAT) gene into duck hepatitis B

virus genome in the place of the polymerase, surface, and pre-surface coding sequences. It was cotransfected with wild-type virus into an avian hepatoma cell line. Culture media containing high titers of the recombinant virus were used to infect primary duckling hepatocytes. Stable CAT gene expression was detected for at least 24 days after transfection (Chang et al., 1991).

5. Non-viral vectors

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In order to effect expression of the oligonucleotide or polynucleotide sequences of the present invention, the expression construct must be delivered into a cell. This delivery may be accomplished *in vitro*, as in laboratory procedures for transforming cells lines, or *in vivo* or *ex vivo*, as in the treatment of certain disease states. As described above, one preferred mechanism for delivery is *via* viral infection where the expression construct is encapsulated in an infectious viral particle.

Once the expression construct has been delivered into the cell the nucleic acid encoding the desired oligonucleotide or polynucleotide sequences may be positioned and expressed at different sites. In certain embodiments, the nucleic acid encoding the construct may be stably integrated into the genome of the cell. This integration may be in the specific location and orientation *via* homologous recombination (gene replacement) or it may be integrated in a random, non-specific location (gene augmentation). In yet further embodiments, the nucleic acid may be stably maintained in the cell as a separate, episomal segment of DNA. Such nucleic acid segments or "episomes" encode sequences sufficient to permit maintenance and replication independent of or in synchronization with the host cell cycle. How the expression construct is delivered to a cell and where in the cell the nucleic acid remains is dependent on the type of expression construct employed.

In certain embodiments of the invention, the expression construct comprising one or more oligonucleotide or polynucleotide sequences may simply consist of naked recombinant DNA or plasmids. Transfer of the construct may be performed by any of the methods mentioned above which physically or chemically permeabilize the cell membrane. This is particularly applicable for transfer *in vitro* but it may be applied to *in vivo* use as well. Dubensky *et al.* (1984) successfully injected

polyomavirus DNA in the form of calcium phosphate precipitates into liver and spleen of adult and newborn mice demonstrating active viral replication and acute infection. Benvenisty and Reshef (1986) also demonstrated that direct intraperitoneal injection of calcium phosphate-precipitated plasmids results in expression of the transfected genes. It is envisioned that DNA encoding a gene of interest may also be transferred in a similar manner *in vivo* and express the gene product.

Another embodiment of the invention for transferring a naked DNA expression construct into cells may involve particle bombardment. This method depends on the ability to accelerate DNA-coated microprojectiles to a high velocity allowing them to pierce cell membranes and enter cells without killing them (Klein et al., 1987). Several devices for accelerating small particles have been developed. One such device relies on a high voltage discharge to generate an electrical current, which in turn provides the motive force (Yang et al., 1990). The microprojectiles used have consisted of biologically inert substances such as tungsten or gold beads.

Selected organs including the liver, skin, and muscle tissue of rats and mice have been bombarded *in vivo* (Yang *et al.*, 1990; Zelenin *et al.*, 1991). This may require surgical exposure of the tissue or cells, to eliminate any intervening tissue between the gun and the target organ, *i.e. ex vivo* treatment. Again, DNA encoding a particular gene may be delivered *via* this method and still be incorporated by the present invention.

ANTISENSE OLIGONUCLEOTIDES

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The end result of the flow of genetic information is the synthesis of protein. DNA is transcribed by polymerases into messenger RNA and translated on the ribosome to yield a folded, functional protein. Thus there are several steps along the route where protein synthesis can be inhibited. The native DNA segment coding for a polypeptide described herein, as all such mammalian DNA strands, has two strands: a sense strand and an antisense strand held together by hydrogen bonding. The messenger RNA coding for polypeptide has the same nucleotide sequence as the sense DNA strand except that the DNA thymidine is replaced by uridine. Thus, synthetic

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antisense nucleotide sequences will bind to a mRNA and inhibit expression of the protein encoded by that mRNA.

The targeting of antisense oligonucleotides to mRNA is thus one mechanism to shut down protein synthesis, and, consequently, represents a powerful and targeted therapeutic approach. For example, the synthesis of polygalactauronase and the muscarine type 2 acetylcholine receptor are inhibited by antisense oligonucleotides directed to their respective mRNA sequences (U. S. Patent 5,739,119 and U. S. Patent 5,759,829, each specifically incorporated herein by reference in its entirety). Further, examples of antisense inhibition have been demonstrated with the nuclear protein cyclin, the multiple drug resistance gene (MDG1), ICAM-1, E-selectin, STK-1, striatal GABA_A receptor and human EGF (Jaskulski *et al.*, 1988; Vasanthakumar and Ahmed, 1989; Peris *et al.*, 1998; U. S. Patent 5,801,154; U. S. Patent 5,789,573; U. S. Patent 5,718,709 and U. S. Patent 5,610,288, each specifically incorporated herein by reference in its entirety). Antisense constructs have also been described that inhibit and can be used to treat a variety of abnormal cellular proliferations, *e.g.* cancer (U. S. Patent 5,747,470; U. S. Patent 5,591,317 and U. S. Patent 5,783,683, each specifically incorporated herein by reference in its entirety).

Therefore, in exemplary embodiments, the invention provides oligonucleotide sequences that comprise all, or a portion of, any sequence that is capable of specifically binding to polynucleotide sequence described herein, or a complement thereof. In one embodiment, the antisense oligonucleotides comprise DNA or derivatives thereof. In another embodiment, the oligonucleotides comprise RNA or derivatives thereof. In a third embodiment, the oligonucleotides are modified DNAs comprising a phosphorothioated modified backbone. In a fourth embodiment, the oligonucleotide sequences comprise peptide nucleic acids or derivatives thereof. In each case, preferred compositions comprise a sequence region that is complementary, and more preferably substantially-complementary, and even more preferably, completely complementary to one or more portions of polynucleotides disclosed herein.

Selection of antisense compositions specific for a given gene sequence is based upon analysis of the chosen target sequence (i.e. in these illustrative examples the rat and human sequences) and determination of secondary structure, T_m , binding

energy, relative stability, and antisense compositions were selected based upon their relative inability to form dimers, hairpins, or other secondary structures that would reduce or prohibit specific binding to the target mRNA in a host cell.

Highly preferred target regions of the mRNA, are those which are at or near the AUG translation initiation codon, and those sequences which were substantially complementary to 5' regions of the mRNA. These secondary structure analyses and target site selection considerations were performed using v.4 of the OLIGO primer analysis software (Rychlik, 1997) and the BLASTN 2.0.5 algorithm software (Altschul *et al.*, 1997).

The use of an antisense delivery method employing a short peptide vector, termed MPG (27 residues), is also contemplated. The MPG peptide contains a hydrophobic domain derived from the fusion sequence of HIV gp41 and a hydrophilic domain from the nuclear localization sequence of SV40 T-antigen (Morris *et al.*, 1997). It has been demonstrated that several molecules of the MPG peptide coat the antisense oligonucleotides and can be delivered into cultured mammalian cells in less than 1 hour with relatively high efficiency (90%). Further, the interaction with MPG strongly increases both the stability of the oligonucleotide to nuclease and the ability to cross the plasma membrane (Morris *et al.*, 1997).

RIBOZYMES

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Although proteins traditionally have been used for catalysis of nucleic acids, another class of macromolecules has emerged as useful in this endeavor. Ribozymes are RNA-protein complexes that cleave nucleic acids in a site-specific fashion. Ribozymes have specific catalytic domains that possess endonuclease activity (Kim and Cech, 1987; Gerlach et al., 1987; Forster and Symons, 1987). For example, a large number of ribozymes accelerate phosphoester transfer reactions with a high degree of specificity, often cleaving only one of several phosphoesters in an oligonucleotide substrate (Cech et al., 1981; Michel and Westhof, 1990; Reinhold-Hurek and Shub, 1992). This specificity has been attributed to the requirement that the substrate bind via specific base-pairing interactions to the internal guide sequence ("IGS") of the ribozyme prior to chemical reaction.

Ribozyme catalysis has primarily been observed as part of sequence-specific cleavage/ligation reactions involving nucleic acids (Joyce, 1989; Cech et al., 1981). For example, U. S. Patent No. 5,354,855 (specifically incorporated herein by reference) reports that certain ribozymes can act as endonucleases with a sequence specificity greater than that of known ribonucleases and approaching that of the DNA restriction enzymes. Thus, sequence-specific ribozyme-mediated inhibition of gene expression may be particularly suited to therapeutic applications (Scanlon et al., 1991; Sarver et al., 1990). Recently, it was reported that ribozymes elicited genetic changes in some cells lines to which they were applied; the altered genes included the oncogenes H-ras, c-fos and genes of HIV. Most of this work involved the modification of a target mRNA, based on a specific mutant codon that is cleaved by a specific ribozyme.

Six basic varieties of naturally-occurring enzymatic RNAs are known presently. Each can catalyze the hydrolysis of RNA phosphodiester bonds *in trans* (and thus can cleave other RNA molecules) under physiological conditions. In general, enzymatic nucleic acids act by first binding to a target RNA. Such binding occurs through the target binding portion of a enzymatic nucleic acid which is held in close proximity to an enzymatic portion of the molecule that acts to cleave the target RNA. Thus, the enzymatic nucleic acid first recognizes and then binds a target RNA through complementary base-pairing, and once bound to the correct site, acts enzymatically to cut the target RNA. Strategic cleavage of such a target RNA will destroy its ability to direct synthesis of an encoded protein. After an enzymatic nucleic acid has bound and cleaved its RNA target, it is released from that RNA to search for another target and can repeatedly bind and cleave new targets.

The enzymatic nature of a ribozyme is advantageous over many technologies, such as antisense technology (where a nucleic acid molecule simply binds to a nucleic acid target to block its translation) since the concentration of ribozyme necessary to affect a therapeutic treatment is lower than that of an antisense oligonucleotide. This advantage reflects the ability of the ribozyme to act enzymatically. Thus, a single ribozyme molecule is able to cleave many molecules of target RNA. In addition, the ribozyme is a highly specific inhibitor, with the specificity of inhibition depending not only on the base pairing mechanism of binding to the target

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RNA, but also on the mechanism of target RNA cleavage. Single mismatches, or base-substitutions, near the site of cleavage can completely eliminate catalytic activity of a ribozyme. Similar mismatches in antisense molecules do not prevent their action (Woolf *et al.*, 1992). Thus, the specificity of action of a ribozyme is greater than that of an antisense oligonucleotide binding the same RNA site.

The enzymatic nucleic acid molecule may be formed in a hammerhead, hairpin, a hepatitis δ virus, group I intron or RNaseP RNA (in association with an RNA guide sequence) or Neurospora VS RNA motif. Examples of hammerhead motifs are described by Rossi et al. (1992). Examples of hairpin motifs are described by Hampel et al. (Eur. Pat. Appl. Publ. No. EP 0360257), Hampel and Tritz (1989), Hampel et al. (1990) and U. S. Patent 5,631,359 (specifically incorporated herein by reference). An example of the hepatitis δ virus motif is described by Perrotta and Been (1992); an example of the RNaseP motif is described by Guerrier-Takada et al. (1983); Neurospora VS RNA ribozyme motif is described by Collins (Saville and Collins, 1990; Saville and Collins, 1991; Collins and Olive, 1993); and an example of the Group I intron is described in (U. S. Patent 4,987,071, specifically incorporated herein by reference). All that is important in an enzymatic nucleic acid molecule of this invention is that it has a specific substrate binding site which is complementary to one or more of the target gene RNA regions, and that it have nucleotide sequences within or surrounding that substrate binding site which impart an RNA cleaving activity to the molecule. Thus the ribozyme constructs need not be limited to specific motifs mentioned herein.

In certain embodiments, it may be important to produce enzymatic cleaving agents which exhibit a high degree of specificity for the RNA of a desired target, such as one of the sequences disclosed herein. The enzymatic nucleic acid molecule is preferably targeted to a highly conserved sequence region of a target mRNA. Such enzymatic nucleic acid molecules can be delivered exogenously to specific cells as required. Alternatively, the ribozymes can be expressed from DNA or RNA vectors that are delivered to specific cells.

Small enzymatic nucleic acid motifs (e.g., of the hammerhead or the hairpin structure) may also be used for exogenous delivery. The simple structure of

these molecules increases the ability of the enzymatic nucleic acid to invade targeted regions of the mRNA structure. Alternatively, catalytic RNA molecules can be expressed within cells from eukaryotic promoters (e.g., Scanlon et al., 1991; Kashani-Sabet et al., 1992; Dropulic et al., 1992; Weerasinghe et al., 1991; Ojwang et al., 1992; Chen et al., 1992; Sarver et al., 1990). Those skilled in the art realize that any ribozyme can be expressed in eukaryotic cells from the appropriate DNA vector. The activity of such ribozymes can be augmented by their release from the primary transcript by a second ribozyme (Int. Pat. Appl. Publ. No. WO 93/23569, and Int. Pat. Appl. Publ. No. WO 94/02595, both hereby incorporated by reference; Ohkawa et al., 1992; Taira et al., 1991; and Ventura et al., 1993).

Ribozymes may be added directly, or can be complexed with cationic lipids, lipid complexes, packaged within liposomes, or otherwise delivered to target cells. The RNA or RNA complexes can be locally administered to relevant tissues ex vivo, or in vivo through injection, aerosol inhalation, infusion pump or stent, with or without their incorporation in biopolymers.

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Ribozymes may be designed as described in Int. Pat. Appl. Publ. No. WO 93/23569 and Int. Pat. Appl. Publ. No. WO 94/02595, each: specifically incorporated herein by reference) and synthesized to be tested *in vitro* and *in vivo*, as described. Such ribozymes can also be optimized for delivery. While specific examples are provided, those in the art will recognize that equivalent RNA targets in other species can be utilized when necessary.

Hammerhead or hairpin ribozymes may be individually analyzed by computer folding (Jaeger et al., 1989) to assess whether the ribozyme sequences fold into the appropriate secondary structure. Those ribozymes with unfavorable intramolecular interactions between the binding arms and the catalytic core are eliminated from consideration. Varying binding arm lengths can be chosen to optimize activity. Generally, at least 5 or so bases on each arm are able to bind to, or otherwise interact with, the target RNA.

Ribozymes of the hammerhead or hairpin motif may be designed to anneal to various sites in the mRNA message, and can be chemically synthesized. The method of synthesis used follows the procedure for normal RNA synthesis as described

in Usman et al. (1987) and in Scaringe et al. (1990) and makes use of common nucleic acid protecting and coupling groups, such as dimethoxytrityl at the 5'-end, and phosphoramidites at the 3'-end. Average stepwise coupling yields are typically >98%. Hairpin ribozymes may be synthesized in two parts and annealed to reconstruct an active ribozyme (Chowrira and Burke, 1992). Ribozymes may be modified extensively to enhance stability by modification with nuclease resistant groups, for example, 2'-amino, 2'-C-allyl, 2'-flouro, 2'-o-methyl, 2'-H (for a review see e.g., Usman and Cedergren, 1992). Ribozymes may be purified by gel electrophoresis using general methods or by high pressure liquid chromatography and resuspended in water.

Ribozyme activity can be optimized by altering the length of the ribozyme binding arms, or chemically synthesizing ribozymes with modifications that prevent their degradation by serum ribonucleases (see e.g., Int. Pat. Appl. Publ. No. WO 92/07065; Perrault et al, 1990; Pieken et al., 1991; Usman and Cedergren, 1992; Int. Pat. Appl. Publ. No. WO 93/15187; Int. Pat. Appl. Publ. No. WO 91/03162; Eur. Pat. Appl. Publ. No. 92110298.4; U. S. Patent 5,334,711; and Int. Pat. Appl. Publ. No. WO 94/13688, which describe various chemical modifications that can be made to the sugar moieties of enzymatic RNA molecules), modifications which enhance their efficacy in cells, and removal of stem II bases to shorten RNA synthesis times and reduce chemical requirements.

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Sullivan et al. (Int. Pat. Appl. Publ. No. WO 94/02595) describes the general methods for delivery of enzymatic RNA molecules. Ribozymes may be administered to cells by a variety of methods known to those familiar to the art, including, but not restricted to, encapsulation in liposomes, by iontophoresis, or by incorporation into other vehicles, such as hydrogels, cyclodextrins, biodegradable nanocapsules, and bioadhesive microspheres. For some indications, ribozymes may be directly delivered ex vivo to cells or tissues with or without the aforementioned vehicles. Alternatively, the RNA/vehicle combination may be locally delivered by direct inhalation, by direct injection or by use of a catheter, infusion pump or stent. Other routes of delivery include, but are not limited to, intravascular, intramuscular, subcutaneous or joint injection, aerosol inhalation, oral (tablet or pill form), topical, systemic, ocular, intraperitoneal and/or intrathecal delivery. More detailed descriptions

of ribozyme delivery and administration are provided in Int. Pat. Appl. Publ. No. WO 94/02595 and Int. Pat. Appl. Publ. No. WO 93/23569, each specifically incorporated herein by reference.

Another means of accumulating high concentrations of a ribozyme(s) within cells is to incorporate the ribozyme-encoding sequences into a DNA expression Transcription of the ribozyme sequences are driven from a promoter for eukaryotic RNA polymerase I (pol I), RNA polymerase II (pol II), or RNA polymerase III (pol III). Transcripts from pol II or pol III promoters will be expressed at high levels in all cells; the levels of a given pol II promoter in a given cell type will depend on the nature of the gene regulatory sequences (enhancers, silencers, etc.) present nearby. Prokaryotic RNA polymerase promoters may also be used, providing that the prokaryotic RNA polymerase enzyme is expressed in the appropriate cells (Elroy-Stein and Moss, 1990; Gao and Huang, 1993; Lieber et al., 1993; Zhou et al., 1990). Ribozymes expressed from such promoters can function in mammalian cells (e.g. Kashani-Saber et al., 1992; Ojwang et al., 1992; Chen et al., 1992; Yu et al., 1993; L'Huillier et al., 1992; Lisziewicz et al., 1993). Such transcription units can be incorporated into a variety of vectors for introduction into mammalian cells, including but not restricted to, plasmid DNA vectors, viral DNA vectors (such as adenovirus or adeno-associated vectors), or viral RNA vectors (such as retroviral, semliki forest virus, sindbis virus vectors).

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Ribozymes may be used as diagnostic tools to examine genetic drift and mutations within diseased cells. They can also be used to assess levels of the target RNA molecule. The close relationship between ribozyme activity and the structure of the target RNA allows the detection of mutations in any region of the molecule which alters the base-pairing and three-dimensional structure of the target RNA. By using multiple ribozymes, one may map nucleotide changes which are important to RNA structure and function *in vitro*, as well as in cells and tissues. Cleavage of target RNAs with ribozymes may be used to inhibit gene expression and define the role (essentially) of specified gene products in the progression of disease. In this manner, other genetic targets may be defined as important mediators of the disease. These studies will lead to better treatment of the disease progression by affording the possibility of combinational

therapies (e.g., multiple ribozymes targeted to different genes, ribozymes coupled with known small molecule inhibitors, or intermittent treatment with combinations of ribozymes and/or other chemical or biological molecules). Other *in vitro* uses of ribozymes are well known in the art, and include detection of the presence of mRNA associated with an IL-5 related condition. Such RNA is detected by determining the presence of a cleavage product after treatment with a ribozyme using standard methodology.

PEPTIDE NUCLEIC ACIDS

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In certain embodiments, the inventors contemplate the use of peptide nucleic acids (PNAs) in the practice of the methods of the invention. PNA is a DNA mimic in which the nucleobases are attached to a pseudopeptide backbone (Good and Nielsen, 1997). PNA is able to be utilized in a number methods that traditionally have used RNA or DNA. Often PNA sequences perform better in techniques than the corresponding RNA or DNA sequences and have utilities that are not inherent to RNA or DNA. A review of PNA including methods of making, characteristics of, and methods of using, is provided by Corey (1997) and is incorporated herein by reference. As such, in certain embodiments, one may prepare PNA sequences that are complementary to one or more portions of the ACE mRNA sequence, and such PNA compositions may be used to regulate, alter, decrease, or reduce the translation of ACE-specific mRNA, and thereby alter the level of ACE activity in a host cell to which such PNA compositions have been administered.

PNAs have 2-aminoethyl-glycine linkages replacing the normal phosphodiester backbone of DNA (Nielsen et al., 1991; Hanvey et al., 1992; Hyrup and Nielsen, 1996; Neilsen, 1996). This chemistry has three important consequences: firstly, in contrast to DNA or phosphorothioate oligonucleotides, PNAs are neutral molecules; secondly, PNAs are achiral, which avoids the need to develop a stereoselective synthesis; and thirdly, PNA synthesis uses standard Boc (Dueholm et al., 1994) or Fmoc (Thomson et al., 1995) protocols for solid-phase peptide synthesis, although other methods, including a modified Merrifield method, have been used (Christensen et al., 1995).

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PNA monomers or ready-made oligomers are commercially available from PerSeptive Biosystems (Framingham, MA). PNA syntheses by either Boc or Fmoc protocols are straightforward using manual or automated protocols (Norton *et al.*, 1995). The manual protocol lends itself to the production of chemically modified PNAs or the simultaneous synthesis of families of closely related PNAs.

As with peptide synthesis, the success of a particular PNA synthesis will depend on the properties of the chosen sequence. For example, while in theory PNAs can incorporate any combination of nucleotide bases, the presence of adjacent purines can lead to deletions of one or more residues in the product. In expectation of this difficulty, it is suggested that, in producing PNAs with adjacent purines, one should repeat the coupling of residues likely to be added inefficiently. This should be followed by the purification of PNAs by reverse-phase high-pressure liquid chromatography (Norton et al., 1995) providing yields and purity of product similar to those observed during the synthesis of peptides.

Modifications of PNAs for a given application may be accomplished by coupling amino acids during solid-phase synthesis or by attaching compounds that contain a carboxylic acid group to the exposed N-terminal amine. Alternatively, PNAs can be modified after synthesis by coupling to an introduced lysine or cysteine. The ease with which PNAs can be modified facilitates optimization for better solubility or for specific functional requirements. Once synthesized, the identity of PNAs and their derivatives can be confirmed by mass spectrometry. Several studies have made and utilized modifications of PNAs (Norton et al., 1995; Haaima et al., 1996; Stetsenko et al., 1996; Petersen et al., 1995; Ulmann et al., 1996; Koch et al., 1995; Orum et al., 1995; Footer et al., 1996; Griffith et al., 1995; Kremsky et al., 1996; Pardridge et al., 1995; Boffa et al., 1997; Landsdorp et al., 1996; Gambacorti-Passerini et al., 1996; Armitage et al., 1997; Seeger et al., 1997; Ruskowski et al., 1997). U.S. Patent No. 5,700,922 discusses PNA-DNA-PNA chimeric molecules and their uses in diagnostics, modulating protein in organisms, and treatment of conditions susceptible to therapeutics.

In contrast to DNA and RNA, which contain negatively charged linkages, the PNA backbone is neutral. In spite of this dramatic alteration, PNAs

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recognize complementary DNA and RNA by Watson-Crick pairing (Egholm *et al.*, 1993), validating the initial modeling by Nielsen *et al.* (1991). PNAs lack 3' to 5' polarity and can bind in either parallel or antiparallel fashion, with the antiparallel mode being preferred (Egholm *et al.*, 1993).

Hybridization of DNA oligonucleotides to DNA and RNA is destabilized by electrostatic repulsion between the negatively charged phosphate backbones of the complementary strands. By contrast, the absence of charge repulsion in PNA-DNA or PNA-RNA duplexes increases the melting temperature (T_m) and reduces the dependence of T_m on the concentration of mono- or divalent cations (Nielsen *et al.*, 1991). The enhanced rate and affinity of hybridization are significant because they are responsible for the surprising ability of PNAs to perform strand invasion of complementary sequences within relaxed double-stranded DNA. In addition, the efficient hybridization at inverted repeats suggests that PNAs can recognize secondary structure effectively within double-stranded DNA. Enhanced recognition also occurs with PNAs immobilized on surfaces, and Wang *et al.* have shown that support-bound PNAs can be used to detect hybridization events (Wang *et al.*, 1996).

One might expect that tight binding of PNAs to complementary sequences would also increase binding to similar (but not identical) sequences, reducing the sequence specificity of PNA recognition. As with DNA hybridization, however, selective recognition can be achieved by balancing oligomer length and incubation temperature. Moreover, selective hybridization of PNAs is encouraged by PNA-DNA hybridization being less tolerant of base mismatches than DNA-DNA hybridization. For example, a single mismatch within a 16 bp PNA-DNA duplex can reduce the $T_{\rm m}$ by up to 15°C (Egholm *et al.*, 1993). This high level of discrimination has allowed the development of several PNA-based strategies for the analysis of point mutations (Wang *et al.*, 1996; Carlsson *et al.*, 1996; Thiede *et al.*, 1996; Webb and Hurskainen, 1996; Perry-O'Keefe *et al.*, 1996).

High-affinity binding provides clear advantages for molecular recognition and the development of new applications for PNAs. For example, 11-13 nucleotide PNAs inhibit the activity of telomerase, a ribonucleo-protein that extends

telomere ends using an essential RNA template, while the analogous DNA oligomers do not (Norton et al., 1996).

Neutral PNAs are more hydrophobic than analogous DNA oligomers, and this can lead to difficulty solubilizing them at neutral pH, especially if the PNAs have a high purine content or if they have the potential to form secondary structures. Their solubility can be enhanced by attaching one or more positive charges to the PNA termini (Nielsen *et al.*, 1991).

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Findings by Allfrey and colleagues suggest that strand invasion will occur spontaneously at sequences within chromosomal DNA (Boffa et al., 1995; Boffa et al., 1996). These studies targeted PNAs to triplet repeats of the nucleotides CAG and used this recognition to purify transcriptionally active DNA (Boffa et al., 1995) and to inhibit transcription (Boffa et al., 1996). This result suggests that if PNAs can be delivered within cells then they will have the potential to be general sequence-specific regulators of gene expression. Studies and reviews concerning the use of PNAs as antisense and anti-gene agents include Nielsen et al. (1993b), Hanvey et al. (1992), and Good and Nielsen (1997). Koppelhus et al. (1997) have used PNAs to inhibit HIV-1 inverse transcription, showing that PNAs may be used for antiviral therapies.

Methods of characterizing the antisense binding properties of PNAs are discussed in Rose (1993) and Jensen *et al.* (1997). Rose uses capillary gel electrophoresis to determine binding of PNAs to their complementary oligonucleotide, measuring the relative binding kinetics and stoichiometry. Similar types of measurements were made by Jensen *et al.* using BIAcoreTM technology.

Other applications of PNAs include use in DNA strand invasion (Nielsen et al., 1991), antisense inhibition (Hanvey et al., 1992), mutational analysis (Orum et al., 1993), enhancers of transcription (Mollegaard et al., 1994), nucleic acid purification (Orum et al., 1995), isolation of transcriptionally active genes (Boffa et al., 1995), blocking of transcription factor binding (Vickers et al., 1995), genome cleavage (Veselkov et al., 1996), biosensors (Wang et al., 1996), in situ hybridization (Thisted et al., 1996), and in a alternative to Southern blotting (Perry-O'Keefe, 1996).

POLYPEPTIDE COMPOSITIONS

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The present invention, in other aspects, provides polypeptide compositions. Generally, a polypeptide of the invention will be an isolated polypeptide (or an epitope, variant, or active fragment thereof) derived from a mammalian species. Preferably, the polypeptide is encoded by a polynucleotide sequence disclosed herein or a sequence which hybridizes under moderately stringent conditions to a polynucleotide sequence disclosed herein. Alternatively, the polypeptide may be defined as a polypeptide which comprises a contiguous amino acid sequence from an amino acid sequence disclosed herein, or which polypeptide comprises an entire amino acid sequence disclosed herein.

In the present invention, a polypeptide composition is also understood to comprise one or more polypeptides that are immunologically reactive with antibodies generated against a polypeptide of the invention, particularly a polypeptide having the amino acid sequence disclosed in SEQ ID NO: 786, 787, 791, 793, 795, 797-799, 806 or 809, or to active fragments, or to variants or biological functional equivalents thereof.

Likewise, a polypeptide composition of the present invention is understood to comprise one or more polypeptides that are capable of eliciting antibodies that are immunologically reactive with one or more polypeptides encoded by one or more contiguous nucleic acid sequences contained in SEQ ID NO: 1, 11-13, 15, 20, 23-27, 29, 30, 33, 34, 39, 41, 43-46, 51, 52, 57, 58, 60, 62, 65-67, 69-71, 74, 76, 79, 80, 84, 86, 89-92, 95, 97, 98, 101, 110, 111, 113-119, 121-128, 130-134, 136, 138, 139, 141, 143, 146-151, 153, 154, 157-160, 162-164, 167-178, 180, 181, 183, 186-190, 192, 193, 195-220, 224, 226-231, 234, 236, 237, 240, 241, 244-246, 248, 254, 255, 261, 262, 266, 270, 275, 280, 282, 283, 288, 289, 290, 292, 295, 301, 303, 304, 309, 311, 341-782, 784, 785, 790, 792, 794, 796, 800-804, 807, 808 and 810-826, or to active fragments, or to variants thereof, or to one or more nucleic acid sequences which hybridize to one or more of these sequences under conditions of moderate to high stringency. Particularly illustrative polypeptides include the amino acid sequences disclosed in SEQ ID NO: 786, 787, 791, 793, 795, 797-799, 806, 809 and 827.

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As used herein, an active fragment of a polypeptide includes a whole or a portion of a polypeptide which is modified by conventional techniques, e.g., mutagenesis, or by addition, deletion, or substitution, but which active fragment exhibits substantially the same structure function, antigenicity, etc., as a polypeptide as described herein.

In certain illustrative embodiments, the polypeptides of the invention will comprise at least an immunogenic portion of a lung tumor protein or a variant thereof, as described herein. As noted above, a "lung tumor protein" is a protein that is expressed by lung tumor cells. Proteins that are lung tumor proteins also react detectably within an immunoassay (such as an ELISA) with antisera from a patient with lung cancer. Polypeptides as described herein may be of any length. Additional sequences derived from the native protein and/or heterologous sequences may be present, and such sequences may (but need not) possess further immunogenic or antigenic properties.

An "immunogenic portion," as used herein is a portion of a protein that is recognized (*i.e.*, specifically bound) by a B-cell and/or T-cell surface antigen receptor. Such immunogenic portions generally comprise at least 5 amino acid residues, more preferably at least 10, and still more preferably at least 20 amino acid residues of a lung tumor protein or a variant thereof. Certain preferred immunogenic portions include peptides in which an N-terminal leader sequence and/or transmembrane domain have been deleted. Other preferred immunogenic portions may contain a small N- and/or C-terminal deletion (*e.g.*, 1-30 amino acids, preferably 5-15 amino acids), relative to the mature protein.

Immunogenic portions may generally be identified using well known techniques, such as those summarized in Paul, *Fundamental Immunology*, 3rd ed., 243-247 (Raven Press, 1993) and references cited therein. Such techniques include screening polypeptides for the ability to react with antigen-specific antibodies, antisera and/or T-cell lines or clones. As used herein, antisera and antibodies are "antigen-specific" if they specifically bind to an antigen (*i.e.*, they react with the protein in an ELISA or other immunoassay, and do not react detectably with unrelated proteins). Such antisera and antibodies may be prepared as described herein, and using well

known techniques. An immunogenic portion of a native lung tumor protein is a portion that reacts with such antisera and/or T-cells at a level that is not substantially less than the reactivity of the full length polypeptide (e.g., in an ELISA and/or T-cell reactivity assay). Such immunogenic portions may react within such assays at a level that is similar to or greater than the reactivity of the full length polypeptide. Such screens may generally be performed using methods well known to those of ordinary skill in the art, such as those described in Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988. For example, a polypeptide may be immobilized on a solid support and contacted with patient sera to allow binding of antibodies within the sera to the immobilized polypeptide. Unbound sera may then be removed and bound antibodies detected using, for example, ¹²⁵I-labeled Protein A.

As noted above, a composition may comprise a variant of a native lung tumor protein. A polypeptide "variant," as used herein, is a polypeptide that differs from a native lung tumor protein in one or more substitutions, deletions, additions and/or insertions, such that the immunogenicity of the polypeptide is not substantially diminished. In other words, the ability of a variant to react with antigen-specific antisera may be enhanced or unchanged, relative to the native protein, or may be diminished by less than 50%, and preferably less than 20%, relative to the native protein. Such variants may generally be identified by modifying one of the above polypeptide sequences and evaluating the reactivity of the modified polypeptide with antigen-specific antibodies or antisera as described herein. Preferred variants include those in which one or more portions, such as an N-terminal leader sequence or transmembrane domain, have been removed. Other preferred variants include variants in which a small portion (e.g., 1-30 amino acids, preferably 5-15 amino acids) has been removed from the N- and/or C-terminal of the mature protein.

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Polypeptide variants encompassed by the present invention include those exhibiting at least about 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% or more identity (determined as described above) to the polypeptides disclosed herein.

Preferably, a variant contains conservative substitutions. A "conservative substitution" is one in which an amino acid is substituted for another

amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydropathic nature of the polypeptide to be substantially unchanged. Amino acid substitutions may generally be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values include leucine, isoleucine and valine; glycine and alanine; asparagine and glutamine; and serine, threonine, phenylalanine and tyrosine. Other groups of amino acids that may represent conservative changes include: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his. A variant may also, or alternatively, contain nonconservative changes. In a preferred embodiment, variant polypeptides differ from a native sequence by substitution, deletion or addition of five amino acids or fewer. Variants may also (or alternatively) be modified by, for example, the deletion or addition of amino acids that have minimal influence on the immunogenicity, secondary structure and hydropathic nature of the polypeptide.

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As noted above, polypeptides may comprise a signal (or leader) sequence at the N-terminal end of the protein, which co-translationally or post-translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (e.g., poly-His), or to enhance binding of the polypeptide to a solid support. For example, a polypeptide may be conjugated to an immunoglobulin Fc region.

Polypeptides may be prepared using any of a variety of well known techniques. Recombinant polypeptides encoded by DNA sequences as described above may be readily prepared from the DNA sequences using any of a variety of expression vectors known to those of ordinary skill in the art. Expression may be achieved in any appropriate host cell that has been transformed or transfected with an expression vector containing a DNA molecule that encodes a recombinant polypeptide. Suitable host cells include prokaryotes, yeast, and higher eukaryotic cells, such as mammalian cells and plant cells. Preferably, the host cells employed are *E. coli*, yeast or a mammalian

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cell line such as COS or CHO. Supernatants from suitable host/vector systems which secrete recombinant protein or polypeptide into culture media may be first concentrated using a commercially available filter. Following concentration, the concentrate may be applied to a suitable purification matrix such as an affinity matrix or an ion exchange resin. Finally, one or more reverse phase HPLC steps can be employed to further purify a recombinant polypeptide.

Portions and other variants having less than about 100 amino acids, and generally less than about 50 amino acids, may also be generated by synthetic means, using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain. See Merrifield, J. Am. Chem. Soc. 85:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Perkin Elmer/Applied BioSystems Division (Foster City, CA), and may be operated according to the manufacturer's instructions.

Within certain specific embodiments, a polypeptide may be a fusion protein that comprises multiple polypeptides as described herein, or that comprises at least one polypeptide as described herein and an unrelated sequence, such as a known tumor protein. A fusion partner may, for example, assist in providing T helper epitopes (an immunological fusion partner), preferably T helper epitopes recognized by humans, or may assist in expressing the protein (an expression enhancer) at higher yields than the native recombinant protein. Certain preferred fusion partners are both immunological and expression enhancing fusion partners. Other fusion partners may be selected so as to increase the solubility of the protein or to enable the protein to be targeted to desired intracellular compartments. Still further fusion partners include affinity tags, which facilitate purification of the protein.

Fusion proteins may generally be prepared using standard techniques, including chemical conjugation. Preferably, a fusion protein is expressed as a recombinant protein, allowing the production of increased levels, relative to a non-fused protein, in an expression system. Briefly, DNA sequences encoding the polypeptide

components may be assembled separately, and ligated into an appropriate expression vector. The 3' end of the DNA sequence encoding one polypeptide component is ligated, with or without a peptide linker, to the 5' end of a DNA sequence encoding the second polypeptide component so that the reading frames of the sequences are in phase. This permits translation into a single fusion protein that retains the biological activity of both component polypeptides.

. A peptide linker sequence may be employed to separate the first and second polypeptide components by a distance sufficient to ensure that each polypeptide folds into its secondary and tertiary structures. Such a peptide linker sequence is incorporated into the fusion protein using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea et al., Gene 40:39-46, 1985; Murphy et al., Proc. Natl. Acad. Sci. USA 83:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent No. 4,751,180. The linker sequence may generally be from 1 to about 50 amino acids in length. Linker sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to separate the functional domains and prevent steric interference.

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The ligated DNA sequences are operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements responsible for expression of DNA are located only 5' to the DNA sequence encoding the first polypeptides. Similarly, stop codons required to end translation and transcription termination signals are only present 3' to the DNA sequence encoding the second polypeptide.

Fusion proteins are also provided. Such proteins comprise a polypeptide as described herein together with an unrelated immunogenic protein. Preferably the

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immunogenic protein is capable of eliciting a recall response. Examples of such proteins include tetanus, tuberculosis and hepatitis proteins (see, for example, Stoute et al. New Engl. J. Med., 336:86-91, 1997).

Within preferred embodiments, an immunological fusion partner is derived from protein D, a surface protein of the gram-negative bacterium Haemophilus influenza B (WO 91/18926). Preferably, a protein D derivative comprises approximately the first third of the protein (e.g., the first N-terminal 100-110 amino acids), and a protein D derivative may be lipidated. Within certain preferred embodiments, the first 109 residues of a Lipoprotein D fusion partner is included on the N-terminus to provide the polypeptide with additional exogenous T-cell epitopes and to increase the expression level in E. coli (thus functioning as an expression enhancer). The lipid tail ensures optimal presentation of the antigen to antigen presenting cells. Other fusion partners include the non-structural protein from influenzae virus, NS1 (hemaglutinin). Typically, the N-terminal 81 amino acids are used, although different fragments that include T-helper epitopes may be used.

In another embodiment, the immunological fusion partner is the protein known as LYTA, or a portion thereof (preferably a C-terminal portion). LYTA is derived from *Streptococcus pneumoniae*, which synthesizes an N-acetyl-L-alanine amidase known as amidase LYTA (encoded by the LytA gene; *Gene 43*:265-292, 1986). LYTA is an autolysin that specifically degrades certain bonds in the peptidoglycan backbone. The C-terminal domain of the LYTA protein is responsible for the affinity to the choline or to some choline analogues such as DEAE. This property has been exploited for the development of *E. coli* C-LYTA expressing plasmids useful for expression of fusion proteins. Purification of hybrid proteins containing the C-LYTA fragment at the amino terminus has been described (*see Biotechnology 10*:795-798, 1992). Within a preferred embodiment, a repeat portion of LYTA may be incorporated into a fusion protein. A repeat portion is found in the C-terminal region starting at residue 178. A particularly preferred repeat portion incorporates residues 188-305.

In general, polypeptides (including fusion proteins) and polynucleotides as described herein are isolated. An "isolated" polypeptide or polynucleotide is one that

is removed from its original environment. For example, a naturally-occurring protein is isolated if it is separated from some or all of the coexisting materials in the natural system. Preferably, such polypeptides are at least about 90% pure, more preferably at least about 95% pure and most preferably at least about 99% pure. A polynucleotide is considered to be isolated if, for example, it is cloned into a vector that is not a part of the natural environment.

BINDING AGENTS

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The present invention further provides agents, such as antibodies and antigen-binding fragments thereof, that specifically bind to a lung tumor protein. As used herein, an antibody, or antigen-binding fragment thereof, is said to "specifically bind" to a lung tumor protein if it reacts at a detectable level (within, for example, an ELISA) with a lung tumor protein, and does not react detectably with unrelated proteins under similar conditions. As used herein, "binding" refers to a noncovalent association between two separate molecules such that a complex is formed. The ability to bind may be evaluated by, for example, determining a binding constant for the formation of the complex. The binding constant is the value obtained when the concentration of the complex is divided by the product of the component concentrations. In general, two compounds are said to "bind," in the context of the present invention, when the binding constant for complex formation exceeds about 10³ L/mol. The binding constant may be determined using methods well known in the art.

Binding agents may be further capable of differentiating between patients with and without a cancer, such as lung cancer, using the representative assays provided herein. In other words, antibodies or other binding agents that bind to a lung tumor protein will generate a signal indicating the presence of a cancer in at least about 20% of patients with the disease, and will generate a negative signal indicating the absence of the disease in at least about 90% of individuals without the cancer. To determine whether a binding agent satisfies this requirement, biological samples (e.g., blood, sera, sputum, urine and/or tumor biopsies) from patients with and without a cancer (as determined using standard clinical tests) may be assayed as described herein for the presence of polypeptides that bind to the binding agent. It will be apparent that a

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statistically significant number of samples with and without the disease should be assayed. Each binding agent should satisfy the above criteria; however, those of ordinary skill in the art will recognize that binding agents may be used in combination to improve sensitivity.

Any agent that satisfies the above requirements may be a binding agent. For example, a binding agent may be a ribosome, with or without a peptide component, an RNA molecule or a polypeptide. In a preferred embodiment, a binding agent is an antibody or an antigen-binding fragment thereof. Antibodies may be prepared by any of a variety of techniques known to those of ordinary skill in the art. See, e.g., Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988. In general, antibodies can be produced by cell culture techniques, including the generation of monoclonal antibodies as described herein, or via transfection of antibody genes into suitable bacterial or mammalian cell hosts, in order to allow for the production of recombinant antibodies. In one technique, an immunogen comprising the polypeptide is initially injected into any of a wide variety of mammals (e.g., mice, rats, rabbits, sheep or goats). In this step, the polypeptides of this invention may serve as the immunogen without modification. Alternatively, particularly for relatively short polypeptides, a superior immune response may be elicited if the polypeptide is joined to a carrier protein, such as bovine serum albumin or keyhole limpet hemocyanin. The immunogen is injected into the animal host, preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically. Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies specific for an antigenic polypeptide of interest may be prepared, for example, using the technique of Kohler and Milstein, Eur. J. Immunol. 6:511-519, 1976, and improvements thereto. Briefly, these methods involve the preparation of immortal cell lines capable of producing antibodies having the desired specificity (i.e., reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a

myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and their culture supernatants tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction. The polypeptides of this invention may be used in the purification process in, for example, an affinity chromatography step.

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Within certain embodiments, the use of antigen-binding fragments of antibodies may be preferred. Such fragments include Fab fragments, which may be prepared using standard techniques. Briefly, immunoglobulins may be purified from rabbit serum by affinity chromatography on Protein A bead columns (Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988) and digested by papain to yield Fab and Fc fragments. The Fab and Fc fragments may be separated by affinity chromatography on protein A bead columns.

Monoclonal antibodies of the present invention may be coupled to one or more therapeutic agents. Suitable agents in this regard include radionuclides, differentiation inducers, drugs, toxins, and derivatives thereof. Preferred radionuclides include ⁹⁰Y, ¹²³I, ¹²⁵I, ¹³¹I, ¹⁸⁶Re, ¹⁸⁸Re, ²¹¹At, and ²¹²Bi. Preferred drugs include methotrexate, and pyrimidine and purine analogs. Preferred differentiation inducers include phorbol esters and butyric acid. Preferred toxins include ricin, abrin, diptheria

toxin, cholera toxin, gelonin, Pseudomonas exotoxin, Shigella toxin, and pokeweed antiviral protein.

A therapeutic agent may be coupled (e.g., covalently bonded) to a suitable monoclonal antibody either directly or indirectly (e.g., via a linker group). A direct reaction between an agent and an antibody is possible when each possesses a substituent capable of reacting with the other. For example, a nucleophilic group, such as an amino or sulfhydryl group, on one may be capable of reacting with a carbonyl-containing group, such as an anhydride or an acid halide, or with an alkyl group containing a good leaving group (e.g., a halide) on the other.

Alternatively, it may be desirable to couple a therapeutic agent and an antibody via a linker group. A linker group can function as a spacer to distance an antibody from an agent in order to avoid interference with binding capabilities. A linker group can also serve to increase the chemical reactivity of a substituent on an agent or an antibody, and thus increase the coupling efficiency. An increase in chemical reactivity may also facilitate the use of agents, or functional groups on agents, which otherwise would not be possible.

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It will be evident to those skilled in the art that a variety of bifunctional or polyfunctional reagents, both homo- and hetero-functional (such as those described in the catalog of the Pierce Chemical Co., Rockford, IL), may be employed as the linker group. Coupling may be effected, for example, through amino groups, carboxyl groups, sulfhydryl groups or oxidized carbohydrate residues. There are numerous references describing such methodology, e.g., U.S. Patent No. 4,671,958, to Rodwell et al.

Where a therapeutic agent is more potent when free from the antibody portion of the immunoconjugates of the present invention, it may be desirable to use a linker group which is cleavable during or upon internalization into a cell. A number of different cleavable linker groups have been described. The mechanisms for the intracellular release of an agent from these linker groups include cleavage by reduction of a disulfide bond (e.g., U.S. Patent No. 4,489,710, to Spitler), by irradiation of a photolabile bond (e.g., U.S. Patent No. 4,625,014, to Senter et al.), by hydrolysis of derivatized amino acid side chains (e.g., U.S. Patent No. 4,638,045, to Kohn et al.), by

serum complement-mediated hydrolysis (e.g., U.S. Patent No. 4,671,958, to Rodwell et al.), and acid-catalyzed hydrolysis (e.g., U.S. Patent No. 4,569,789, to Blattler et al.).

It may be desirable to couple more than one agent to an antibody. In one embodiment, multiple molecules of an agent are coupled to one antibody molecule. In another embodiment, more than one type of agent may be coupled to one antibody. Regardless of the particular embodiment, immunoconjugates with more than one agent may be prepared in a variety of ways. For example, more than one agent may be coupled directly to an antibody molecule, or linkers that provide multiple sites for attachment can be used. Alternatively, a carrier can be used.

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A carrier may bear the agents in a variety of ways, including covalent bonding either directly or via a linker group. Suitable carriers include proteins such as albumins (e.g., U.S. Patent No. 4,507,234, to Kato et al.), peptides and polysaccharides such as aminodextran (e.g., U.S. Patent No. 4,699,784, to Shih et al.). A carrier may also bear an agent by noncovalent bonding or by encapsulation, such as within a liposome vesicle (e.g., U.S. Patent Nos. 4,429,008 and 4,873,088). Carriers specific for radionuclide agents include radiohalogenated small molecules and chelating compounds. For example, U.S. Patent No. 4,735,792 discloses representative radiohalogenated small molecules and their synthesis. A radionuclide chelate may be formed from chelating compounds that include those containing nitrogen and sulfur atoms as the donor atoms for binding the metal, or metal oxide, radionuclide. For example, U.S. Patent No. 4,673,562, to Davison et al. discloses representative chelating compounds and their synthesis.

A variety of routes of administration for the antibodies and immunoconjugates may be used. Typically, administration will be intravenous, intramuscular, subcutaneous or in the bed of a resected tumor. It will be evident that the precise dose of the antibody/immunoconjugate will vary depending upon the antibody used, the antigen density on the tumor, and the rate of clearance of the antibody.

T CELLS

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Immunotherapeutic compositions may also, or alternatively, comprise T cells specific for a lung tumor protein. Such cells may generally be prepared *in vitro* or *ex vivo*, using standard procedures. For example, T cells may be isolated from bone marrow, peripheral blood, or a fraction of bone marrow or peripheral blood of a patient, using a commercially available cell separation system, such as the IsolexTM System, available from Nexell Therapeutics, Inc. (Irvine, CA; see also U.S. Patent No. 5,240,856; U.S. Patent No. 5,215,926; WO 89/06280; WO 91/16116 and WO 92/07243). Alternatively, T cells may be derived from related or unrelated humans, non-human mammals, cell lines or cultures.

T cells may be stimulated with a lung tumor polypeptide, polynucleotide encoding a lung tumor polypeptide and/or an antigen presenting cell (APC) that expresses such a polypeptide. Such stimulation is performed under conditions and for a time sufficient to permit the generation of T cells that are specific for the polypeptide. Preferably, a lung tumor polypeptide or polynucleotide is present within a delivery vehicle, such as a microsphere, to facilitate the generation of specific T cells.

T cells are considered to be specific for a lung tumor polypeptide if the T cells specifically proliferate, secrete cytokines or kill target cells coated with the polypeptide or expressing a gene encoding the polypeptide. T cell specificity may be evaluated using any of a variety of standard techniques. For example, within a chromium release assay or proliferation assay, a stimulation index of more than two fold increase in lysis and/or proliferation, compared to negative controls, indicates T cell specificity. Such assays may be performed, for example, as described in Chen *et al.*, *Cancer Res.* 54:1065-1070, 1994. Alternatively, detection of the proliferation of T cells may be accomplished by a variety of known techniques. For example, T cell proliferation can be detected by measuring an increased rate of DNA synthesis (*e.g.*, by pulse-labeling cultures of T cells with tritiated thymidine and measuring the amount of tritiated thymidine incorporated into DNA). Contact with a lung tumor polypeptide (100 ng/ml - 100 μg/ml, preferably 200 ng/ml - 25 μg/ml) for 3 - 7 days should result in at least a two fold increase in proliferation of the T cells. Contact as described above for 2-3 hours should result in activation of the T cells, as measured using standard

cytokine assays in which a two fold increase in the level of cytokine release (e.g., TNF or IFN-γ) is indicative of T cell activation (see Coligan et al., Current Protocols in Immunology, vol. 1, Wiley Interscience (Greene 1998)). T cells that have been activated in response to a lung tumor polypeptide, polynucleotide or polypeptide-expressing APC may be CD4⁺ and/or CD8⁺. Lung tumor protein-specific T cells may be expanded using standard techniques. Within preferred embodiments, the T cells are derived from a patient, a related donor or an unrelated donor, and are administered to the patient following stimulation and expansion.

For therapeutic purposes, CD4⁺ or CD8⁺ T cells that proliferate in response to a lung tumor polypeptide, polynucleotide or APC can be expanded in number either *in vitro* or *in vivo*. Proliferation of such T cells *in vitro* may be accomplished in a variety of ways. For example, the T cells can be re-exposed to a lung tumor polypeptide, or a short peptide corresponding to an immunogenic portion of such a polypeptide, with or without the addition of T cell growth factors, such as interleukin-2, and/or stimulator cells that synthesize a lung tumor polypeptide. Alternatively, one or more T cells that proliferate in the presence of a lung tumor protein can be expanded in number by cloning. Methods for cloning cells are well known in the art, and include limiting dilution.

PHARMACEUTICAL COMPOSITIONS

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In additional embodiments, the present invention concerns formulation of one or more of the polynucleotide, polypeptide, T-cell and/or antibody compositions disclosed herein in pharmaceutically-acceptable solutions for administration to a cell or an animal, either alone, or in combination with one or more other modalities of therapy.

It will also be understood that, if desired, the nucleic acid segment, RNA, DNA or PNA compositions that express a polypeptide as disclosed herein may be administered in combination with other agents as well, such as, e.g., other proteins or polypeptides or various pharmaceutically-active agents. In fact, there is virtually no limit to other components that may also be included, given that the additional agents do not cause a significant adverse effect upon contact with the target cells or host tissues. The compositions may thus be delivered along with various other agents as required in

the particular instance. Such compositions may be purified from host cells or other biological sources, or alternatively may be chemically synthesized as described herein. Likewise, such compositions may further comprise substituted or derivatized RNA or DNA compositions.

Formulation of pharmaceutically-acceptable excipients and carrier solutions is well-known to those of skill in the art, as is the development of suitable dosing and treatment regimens for using the particular compositions described herein in a variety of treatment regimens, including *e.g.*, oral, parenteral, intravenous, intranasal, and intramuscular administration and formulation.

10 1. ORAL DELIVERY

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In certain applications, the pharmaceutical compositions disclosed herein may be delivered *via* oral administration to an animal. As such, these compositions may be formulated with an inert diluent or with an assimilable edible carrier, or they may be enclosed in hard- or soft-shell gelatin capsule, or they may be compressed into tablets, or they may be incorporated directly with the food of the diet.

The active compounds may even be incorporated with excipients and used in the form of ingestible tablets, buccal tables, troches, capsules, elixirs, suspensions, syrups, wafers, and the like (Mathiowitz et al., 1997; Hwang et al., 1998; U. S. Patent 5,641,515; U. S. Patent 5,580,579 and U. S. Patent 5,792,451, each specifically incorporated herein by reference in its entirety). The tablets, troches, pills, capsules and the like may also contain the following: a binder, as gum tragacanth, acacia, cornstarch, or gelatin; excipients, such as dicalcium phosphate; a disintegrating agent, such as corn starch, potato starch, alginic acid and the like; a lubricant, such as magnesium stearate; and a sweetening agent, such as sucrose, lactose or saccharin may be added or a flavoring agent, such as peppermint, oil of wintergreen, or cherry flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar, or both. A syrup of elixir may contain the active compound sucrose as a sweetening agent methyl and

propylparabens as preservatives, a dye and flavoring, such as cherry or orange flavor. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active compounds may be incorporated into sustained-release preparation and formulations.

Typically, these formulations may contain at least about 0.1% of the active compound or more, although the percentage of the active ingredient(s) may, of course, be varied and may conveniently be between about 1 or 2% and about 60% or 70% or more of the weight or volume of the total formulation. Naturally, the amount of active compound(s) in each therapeutically useful composition may be prepared is such a way that a suitable dosage will be obtained in any given unit dose of the compound. Factors such as solubility, bioavailability, biological half-life, route of administration, product shelf life, as well as other pharmacological considerations will be contemplated by one skilled in the art of preparing such pharmaceutical formulations, and as such, a variety of dosages and treatment regimens may be desirable.

For oral administration the compositions of the present invention may alternatively be incorporated with one or more excipients in the form of a mouthwash, dentifrice, buccal tablet, oral spray, or sublingual orally-administered formulation. For example, a mouthwash may be prepared incorporating the active ingredient in the required amount in an appropriate solvent, such as a sodium borate solution (Dobell's Solution). Alternatively, the active ingredient may be incorporated into an oral solution such as one containing sodium borate, glycerin and potassium bicarbonate, or dispersed in a dentifrice, or added in a therapeutically-effective amount to a composition that may include water, binders, abrasives, flavoring agents, foaming agents, and humectants. Alternatively the compositions may be fashioned into a tablet or solution form that may be placed under the tongue or otherwise dissolved in the mouth.

2. INJECTABLE DELIVERY

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In certain circumstances it will be desirable to deliver the pharmaceutical compositions disclosed herein parenterally, intravenously, intramuscularly, or even intraperitoneally as described in U. S. Patent 5,543,158; U. S. Patent 5,641,515 and U.

S. Patent 5,399,363 (each specifically incorporated herein by reference in its entirety). Solutions of the active compounds as free base or pharmacologically acceptable salts may be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions may also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

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The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions (U. S. Patent 5,466,468, specifically incorporated herein by reference in its entirety). In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and/or vegetable oils. Proper fluidity may be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be facilitated by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

For parenteral administration in an aqueous solution, for example, the solution should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. In this connection, a sterile aqueous medium that can be employed will be known to those of skill in the art in light of the present disclosure. For example, one

dosage may be dissolved in 1 ml of isotonic NaCl solution and either added to 1000 ml of hypodermoclysis fluid or injected at the proposed site of infusion, (see for example, "Remington's Pharmaceutical Sciences" 15th Edition, pages 1035-1038 and 1570-1580). Some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject. Moreover, for human administration, preparations should meet sterility, pyrogenicity, and the general safety and purity standards as required by FDA Office of Biologics standards.

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Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

The compositions disclosed herein may be formulated in a neutral or salt form. Pharmaceutically-acceptable salts, include the acid addition salts (formed with the free amino groups of the protein) and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like. Upon formulation, solutions will be administered in a manner compatible with the dosage formulation and in such amount as is therapeutically effective. The formulations are easily administered in a variety of dosage forms such as injectable solutions, drug-release capsules, and the like.

As used herein, "carrier" includes any and all solvents, dispersion media, vehicles, coatings, diluents, antibacterial and antifungal agents, isotonic and absorption

delaying agents, buffers, carrier solutions, suspensions, colloids, and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

The phrase "pharmaceutically-acceptable" refers to molecular entities and compositions that do not produce an allergic or similar untoward reaction when administered to a human. The preparation of an aqueous composition that contains a protein as an active ingredient is well understood in the art. Typically, such compositions are prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for solution in, or suspension in, liquid prior to injection can also be prepared. The preparation can also be emulsified.

3. NASAL DELIVERY

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In certain embodiments, the pharmaceutical compositions may be delivered by intranasal sprays, inhalation, and/or other aerosol delivery vehicles. Methods for delivering genes, nucleic acids, and peptide compositions directly to the lungs via nasal aerosol sprays has been described e.g., in U. S. Patent 5,756,353 and U. S. Patent 5,804,212 (each specifically incorporated herein by reference in its entirety). Likewise, the delivery of drugs using intranasal microparticle resins (Takenaga et al., 1998) and lysophosphatidyl-glycerol compounds (U. S. Patent 5,725,871, specifically incorporated herein by reference in its entirety) are also well-known in the pharmaceutical arts. Likewise, transmucosal drug delivery in the form of a polytetrafluoroetheylene support matrix is described in U. S. Patent 5,780,045 (specifically incorporated herein by reference in its entirety).

25 4. LIPOSOME-, NANOCAPSULE-, AND MICROPARTICLE-MEDIATED DELIVERY

In certain embodiments, the inventors contemplate the use of liposomes, nanocapsules, microparticles, microspheres, lipid particles, vesicles, and the like, for the introduction of the compositions of the present invention into suitable host cells. In particular, the compositions of the present invention may be formulated for delivery

either encapsulated in a lipid particle, a liposome, a vesicle, a nanosphere, or a nanoparticle or the like.

Such formulations may be preferred for the introduction of pharmaceutically-acceptable formulations of the nucleic acids or constructs disclosed herein. The formation and use of liposomes is generally known to those of skill in the art (see for example, Couvreur et al., 1977; Couvreur, 1988; Lasic, 1998; which describes the use of liposomes and nanocapsules in the targeted antibiotic therapy for intracellular bacterial infections and diseases). Recently, liposomes were developed improved circulation half-times serum stability and (Gabizon with Papahadjopoulos, 1988; Allen and Choun, 1987; U. S. Patent 5,741,516, specifically incorporated herein by reference in its entirety). Further, various methods of liposome and liposome like preparations as potential drug carriers have been reviewed (Takakura, 1998; Chandran et al., 1997; Margalit, 1995; U. S. Patent 5,567,434; U. S. Patent 5,552,157; U. S. Patent 5,565,213; U. S. Patent 5,738,868 and U. S. Patent 5,795,587, each specifically incorporated herein by reference in its entirety).

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Liposomes have been used successfully with a number of cell types that are normally resistant to transfection by other procedures including T cell suspensions, primary hepatocyte cultures and PC 12 cells (Renneisen et al., 1990; Muller et al., 1990). In addition, liposomes are free of the DNA length constraints that are typical of viral-based delivery systems. Liposomes have been used effectively to introduce genes, drugs (Heath and Martin, 1986; Heath et al., 1986; Balazsovits et al., 1989; Fresta and Puglisi, 1996), radiotherapeutic agents (Pikul et al., 1987), enzymes (Imaizumi et al., 1990a; Imaizumi et al., 1990b), viruses (Faller and Baltimore, 1984), transcription factors and allosteric effectors (Nicolau and Gersonde, 1979) into a variety of cultured cell lines and animals. In addition, several successful clinical trails examining the effectiveness of liposome-mediated drug delivery have been completed (Lopez-Berestein et al., 1985a; 1985b; Coune, 1988; Sculier et al., 1988). Furthermore, several studies suggest that the use of liposomes is not associated with autoimmune responses, toxicity or gonadal localization after systemic delivery (Mori and Fukatsu, 1992).

Liposomes are formed from phospholipids that are dispersed in an aqueous medium and spontaneously form multilamellar concentric bilayer vesicles

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(also termed multilamellar vesicles (MLVs). MLVs generally have diameters of from 25 nm to 4 μ m. Sonication of MLVs results in the formation of small unilamellar vesicles (SUVs) with diameters in the range of 200 to 500 Å, containing an aqueous solution in the core.

Liposomes bear resemblance to cellular membranes and are contemplated for use in connection with the present invention as carriers for the peptide compositions. They are widely suitable as both water- and lipid-soluble substances can be entrapped, *i.e.* in the aqueous spaces and within the bilayer itself, respectively. It is possible that the drug-bearing liposomes may even be employed for site-specific delivery of active agents by selectively modifying the liposomal formulation.

In addition to the teachings of Couvreur et al. (1977; 1988), the following information may be utilized in generating liposomal formulations. Phospholipids can form a variety of structures other than liposomes when dispersed in water, depending on the molar ratio of lipid to water. At low ratios the liposome is the preferred structure. The physical characteristics of liposomes depend on pH, ionic strength and the presence of divalent cations. Liposomes can show low permeability to ionic and polar substances, but at elevated temperatures undergo a phase transition which markedly alters their permeability. The phase transition involves a change from a closely packed, ordered structure, known as the gel state, to a loosely packed, lessordered structure, known as the fluid state. This occurs at a characteristic phase-transition temperature and results in an increase in permeability to ions, sugars and drugs.

In addition to temperature, exposure to proteins can alter the permeability of liposomes. Certain soluble proteins, such as cytochrome c, bind, deform and penetrate the bilayer, thereby causing changes in permeability. Cholesterol inhibits this penetration of proteins, apparently by packing the phospholipids more tightly. It is contemplated that the most useful liposome formations for antibiotic and inhibitor delivery will contain cholesterol.

The ability to trap solutes varies between different types of liposomes.

30 For example, MLVs are moderately efficient at trapping solutes, but SUVs are extremely inefficient. SUVs offer the advantage of homogeneity and reproducibility in

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size distribution, however, and a compromise between size and trapping efficiency is offered by large unilamellar vesicles (LUVs). These are prepared by ether evaporation and are three to four times more efficient at solute entrapment than MLVs.

In addition to liposome characteristics, an important determinant in entrapping compounds is the physicochemical properties of the compound itself. Polar compounds are trapped in the aqueous spaces and nonpolar compounds bind to the lipid bilayer of the vesicle. Polar compounds are released through permeation or when the bilayer is broken, but nonpolar compounds remain affiliated with the bilayer unless it is disrupted by temperature or exposure to lipoproteins. Both types show maximum efflux rates at the phase transition temperature.

Liposomes interact with cells *via* four different mechanisms: endocytosis by phagocytic cells of the reticuloendothelial system such as macrophages and neutrophils; adsorption to the cell surface, either by nonspecific weak hydrophobic or electrostatic forces, or by specific interactions with cell-surface components; fusion with the plasma cell membrane by insertion of the lipid bilayer of the liposome into the plasma membrane, with simultaneous release of liposomal contents into the cytoplasm; and by transfer of liposomal lipids to cellular or subcellular membranes, or vice versa, without any association of the liposome contents. It often is difficult to determine which mechanism is operative and more than one may operate at the same time.

The fate and disposition of intravenously injected liposomes depend on their physical properties, such as size, fluidity, and surface charge. They may persist in tissues for h or days, depending on their composition, and half lives in the blood range from min to several h. Larger liposomes, such as MLVs and LUVs, are taken up rapidly by phagocytic cells of the reticuloendothelial system, but physiology of the circulatory system restrains the exit of such large species at most sites. They can exit only in places where large openings or pores exist in the capillary endothelium, such as the sinusoids of the liver or spleen. Thus, these organs are the predominate site of uptake. On the other hand, SUVs show a broader tissue distribution but still are sequestered highly in the liver and spleen. In general, this *in vivo* behavior limits the potential targeting of liposomes to only those organs and tissues accessible to their large size. These include the blood, liver, spleen, bone marrow, and lymphoid organs.

Targeting is generally not a limitation in terms of the present invention. However, should specific targeting be desired, methods are available for this to be accomplished. Antibodies may be used to bind to the liposome surface and to direct the antibody and its drug contents to specific antigenic receptors located on a particular cell-type surface. Carbohydrate determinants (glycoprotein or glycolipid cell-surface components that play a role in cell-cell recognition, interaction and adhesion) may also be used as recognition sites as they have potential in directing liposomes to particular cell types. Mostly, it is contemplated that intravenous injection of liposomal preparations would be used, but other routes of administration are also conceivable.

Alternatively, the invention provides for pharmaceutically-acceptable nanocapsule formulations of the compositions of the present invention. Nanocapsules can generally entrap compounds in a stable and reproducible way (Henry-Michelland et al., 1987; Quintanar-Guerrero et al., 1998; Douglas et al., 1987). To avoid side effects due to intracellular polymeric overloading, such ultrafine particles (sized around 0.1 µm) should be designed using polymers able to be degraded in vivo. Biodegradable polyalkyl-cyanoacrylate nanoparticles that meet these requirements are contemplated for use in the present invention. Such particles may be are easily made, as described (Couvreur et al., 1980; 1988; zur Muhlen et al., 1998; Zambaux et al. 1998; Pinto-Alphandry et al., 1995 and U. S. Patent 5,145,684, specifically incorporated herein by reference in its entirety).

IMMUNOGENIC COMPOSITIONS

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In certain preferred embodiments of the present invention, immunogenic compositions, or vaccines, are provided. The immunogenic compositions will generally comprise one or more pharmaceutical compositions, such as those discussed above, in combination with an immunostimulant. An immunostimulant may be any substance that enhances or potentiates an immune response (antibody and/or cell-mediated) to an exogenous antigen. Examples of immunostimulants include adjuvants, biodegradable microspheres (e.g., polylactic galactide) and liposomes (into which the compound is incorporated; see e.g., Fullerton, U.S. Patent No. 4,235,877). Vaccine preparation is generally described in, for example, M.F. Powell and M.J. Newman, eds., "Vaccine

Design (the subunit and adjuvant approach)," Plenum Press (NY, 1995). Pharmaceutical compositions and immunogenic compositions, or vaccines, within the scope of the present invention may also contain other compounds, which may be biologically active or inactive. For example, one or more immunogenic portions of other tumor antigens may be present, either incorporated into a fusion polypeptide or as a separate compound, within the composition.

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Illustrative immunogenic compositions may contain DNA encoding one or more of the polypeptides as described above, such that the polypeptide is generated in situ. As noted above, the DNA may be present within any of a variety of delivery systems known to those of ordinary skill in the art, including nucleic acid expression systems, bacteria and viral expression systems. Numerous gene delivery techniques are well known in the art, such as those described by Rolland, Crit. Rev. Therap. Drug Carrier Systems 15:143-198, 1998, and references cited therein. Appropriate nucleic acid expression systems contain the necessary DNA sequences for expression in the patient (such as a suitable promoter and terminating signal). Bacterial delivery systems involve the administration of a bacterium (such as Bacillus-Calmette-Guerrin) that expresses an immunogenic portion of the polypeptide on its cell surface or secretes such an epitope. In a preferred embodiment, the DNA may be introduced using a viral expression system (e.g., vaccinia or other pox virus, retrovirus, or adenovirus), which may involve the use of a non-pathogenic (defective), replication competent virus. Suitable systems are disclosed, for example, in Fisher-Hoch et al., Proc. Natl. Acad. Sci. USA 86:317-321, 1989; Flexner et al., Ann. N.Y. Acad. Sci. 569:86-103, 1989; Flexner et al., Vaccine 8:17-21, 1990; U.S. Patent Nos. 4,603,112, 4,769,330, and 5.017.487; WO 89/01973; U.S. Patent No. 4,777,127; GB 2,200,651; EP 0,345,242; WO 91/02805; Berkner, Biotechniques 6:616-627, 1988; Rosenfeld et al., Science 252:431-434, 1991; Kolls et al., Proc. Natl. Acad. Sci. USA 91:215-219, 1994; Kass-Eisler et al., Proc. Natl. Acad. Sci. USA 90:11498-11502, 1993; Guzman et al., Circulation 88:2838-2848, 1993; and Guzman et al., Cir. Res. 73:1202-1207, 1993. Techniques for incorporating DNA into such expression systems are well known to those of ordinary skill in the art. The DNA may also be "naked," as described, for example, in Ulmer et al., Science 259:1745-1749, 1993 and reviewed by Cohen,

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Science 259:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable beads, which are efficiently transported into the cells. It will be apparent that an immunogenic composition may comprise both a polynucleotide and a polypeptide component. Such immunogenic compositions may provide for an enhanced immune response.

It will be apparent that an immunogenic composition may contain pharmaceutically acceptable salts of the polynucleotides and polypeptides provided herein. Such salts may be prepared from pharmaceutically acceptable non-toxic bases, including organic bases (e.g., salts of primary, secondary and tertiary amines and basic amino acids) and inorganic bases (e.g., sodium, potassium, lithium, ammonium, calcium and magnesium salts).

While any suitable carrier known to those of ordinary skill in the art may be employed in the immunogenic compositions of this invention, the type of carrier will vary depending on the mode of administration. Compositions of the present invention may be formulated for any appropriate manner of administration, including for example, topical, oral, nasal, intravenous, intracranial, intraperitoneal, subcutaneous or intramuscular administration. For parenteral administration, such as subcutaneous injection, the carrier preferably comprises water, saline, alcohol, a fat, a wax or a buffer. For oral administration, any of the above carriers or a solid carrier, such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, sucrose, and magnesium carbonate, may be employed. Biodegradable microspheres (e.g., polylactate polyglycolate) may also be employed as carriers for the pharmaceutical compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268; 5,075,109; 5,928,647; 5,811,128; 5,820,883; 5,853,763; 5,814,344 and 5,942,252. One may also employ a carrier comprising the particulate-protein complexes described in U.S. Patent No. 5,928,647, which are capable of inducing a class I-restricted cytotoxic T lymphocyte responses in a host.

Such compositions may also comprise buffers (e.g., neutral buffered saline or phosphate buffered saline), carbohydrates (e.g., glucose, mannose, sucrose or dextrans), mannitol, proteins, polypeptides or amino acids such as glycine, antioxidants,

bacteriostats, chelating agents such as EDTA or glutathione, adjuvants (e.g., aluminum hydroxide), solutes that render the formulation isotonic, hypotonic or weakly hypertonic with the blood of a recipient, suspending agents, thickening agents and/or preservatives. Alternatively, compositions of the present invention may be formulated as a lyophilizate. Compounds may also be encapsulated within liposomes using well known technology.

Any of a variety of immunostimulants may be employed in the immunogenic compositions of this invention. For example, an adjuvant may be included. Most adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a stimulator of immune responses, such as lipid A, *Bortadella pertussis* or *Mycobacterium tuberculosis* derived proteins. Suitable adjuvants are commercially available as, for example, Freund's Incomplete Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, MI); Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ); AS-2 (SmithKline Beecham, Philadelphia, PA); aluminum salts such as aluminum hydroxide gel (alum) or aluminum phosphate; salts of calcium, iron or zinc; an insoluble suspension of acylated tyrosine; acylated sugars; cationically or anionically derivatized polysaccharides; polyphosphazenes; biodegradable microspheres; monophosphoryl lipid A and quil A. Cytokines, such as GM-CSF or interleukin-2, -7, or -12, may also be used as adjuvants.

Within the immunogenic compositions provided herein, the adjuvant composition is preferably designed to induce an immune response predominantly of the Th1 type. High levels of Th1-type cytokines (e.g., IFN-γ, TNFα, IL-2 and IL-12) tend to favor the induction of cell mediated immune responses to an administered antigen. In contrast, high levels of Th2-type cytokines (e.g., IL-4, IL-5, IL-6 and IL-10) tend to favor the induction of humoral immune responses. Following application of an immunogenic composition as provided herein, a patient will support an immune response that includes Th1- and Th2-type responses. Within a preferred embodiment, in which a response is predominantly Th1-type, the level of Th1-type cytokines will increase to a greater extent than the level of Th2-type cytokines. The levels of these cytokines may be readily assessed using standard assays. For a review of the families of cytokines, see Mosmann and Coffman, Ann. Rev. Immunol. 7:145-173, 1989.

Preferred adjuvants for use in eliciting a predominantly Th1-type response include, for example, a combination of monophosphoryl lipid A, preferably 3de-O-acylated monophosphoryl lipid A (3D-MPL), together with an aluminum salt. MPL adjuvants are available from Corixa Corporation (Seattle, WA; see US Patent Nos. 4,436,727; 4,877,611; 4,866,034 and 4,912,094). CpG-containing oligonucleotides (in which the CpG dinucleotide is unmethylated) also induce a predominantly Th1 response. Such oligonucleotides are well known and are described, for example, in WO 96/02555, WO 99/33488 and U.S. Patent Nos. 6,008,200 and 5,856,462. Immunostimulatory DNA sequences are also described, for example, by Sato et al., Science 273:352, 1996. Another preferred adjuvant is a saponin, preferably QS21 (Aquila Biopharmaceuticals Inc., Framingham, MA), which may be used alone or in combination with other adjuvants. For example, an enhanced system involves the combination of a monophosphoryl lipid A and saponin derivative, such as the combination of QS21 and 3D-MPL as described in WO 94/00153, or a less reactogenic composition where the QS21 is quenched with cholesterol, as described in WO Other preferred formulations comprise an oil-in-water emulsion and 96/33739. tocopherol. A particularly potent adjuvant formulation involving QS21, 3D-MPL and tocopherol in an oil-in-water emulsion is described in WO 95/17210.

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Other preferred adjuvants include Montanide ISA 720 (Seppic, France),

SAF (Chiron, California, United States), ISCOMS (CSL), MF-59 (Chiron), the SBAS series of adjuvants (e.g., SBAS-2 or SBAS-4, available from SmithKline Beecham, Rixensart, Belgium), Detox (Corixa, Hamilton, MT), RC-529 (Corixa, Hamilton, MT) and other aminoalkyl glucosaminide 4-phosphates (AGPs), such as those described in pending U.S. Patent Application Serial Nos. 08/853,826 and 09/074,720, the disclosures of which are incorporated herein by reference in their entireties.

Any immunogenic composition provided herein may be prepared using well known methods that result in a combination of antigen, immune response enhancer and a suitable carrier or excipient. The compositions described herein may be administered as part of a sustained release formulation (*i.e.*, a formulation such as a capsule, sponge or gel (composed of polysaccharides, for example) that effects a slow release of compound following administration). Such formulations may generally be

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prepared using well known technology (see, e.g., Coombes et al., Vaccine 14:1429-1438, 1996) and administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at the desired target site. Sustained-release formulations may contain a polypeptide, polynucleotide or antibody dispersed in a carrier matrix and/or contained within a reservoir surrounded by a rate controlling membrane.

Carriers for use within such formulations are biocompatible, and may also be biodegradable; preferably the formulation provides a relatively constant level of active component release. Such carriers include microparticles of poly(lactide-coglycolide), polyacrylate, latex, starch, cellulose, dextran and the like. Other delayed-release carriers include supramolecular biovectors, which comprise a non-liquid hydrophilic core (e.g., a cross-linked polysaccharide or oligosaccharide) and, optionally, an external layer comprising an amphiphilic compound, such as a phospholipid (see e.g., U.S. Patent No. 5,151,254 and PCT applications WO 94/20078, WO/94/23701 and WO 96/06638). The amount of active compound contained within a sustained release formulation depends upon the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

Any of a variety of delivery vehicles may be employed within pharmaceutical compositions and immunogenic compositions to facilitate production of an antigen-specific immune response that targets tumor cells. Delivery vehicles include antigen presenting cells (APCs), such as dendritic cells, macrophages, B cells, monocytes and other cells that may be engineered to be efficient APCs. Such cells may, but need not, be genetically modified to increase the capacity for presenting the antigen, to improve activation and/or maintenance of the T cell response, to have antitumor effects *per se* and/or to be immunologically compatible with the receiver (*i.e.*, matched HLA haplotype). APCs may generally be isolated from any of a variety of biological fluids and organs, including tumor and peritumoral tissues, and may be autologous, allogeneic, syngeneic or xenogeneic cells.

Certain preferred embodiments of the present invention use dendritic cells or progenitors thereof as antigen-presenting cells. Dendritic cells are highly potent APCs (Banchereau and Steinman, *Nature 392*:245-251, 1998) and have been shown to

be effective as a physiological adjuvant for eliciting prophylactic or therapeutic antitumor immunity (see Timmerman and Levy, Ann. Rev. Med. 50:507-529, 1999). In general, dendritic cells may be identified based on their typical shape (stellate in situ, with marked cytoplasmic processes (dendrites) visible in vitro), their ability to take up, process and present antigens with high efficiency and their ability to activate naïve T cell responses. Dendritic cells may, of course, be engineered to express specific cell-surface receptors or ligands that are not commonly found on dendritic cells in vivo or ex vivo, and such modified dendritic cells are contemplated by the present invention. As an alternative to dendritic cells, secreted vesicles antigen-loaded dendritic cells (called exosomes) may be used within a vaccine, or immunogenic composition (see Zitvogel et al., Nature Med. 4:594-600, 1998).

Dendritic cells and progenitors may be obtained from peripheral blood, bone marrow, tumor-infiltrating cells, peritumoral tissues-infiltrating cells, lymph nodes, spleen, skin, umbilical cord blood or any other suitable tissue or fluid. For example, dendritic cells may be differentiated *ex vivo* by adding a combination of cytokines such as GM-CSF, IL-4, IL-13 and/or TNFα to cultures of monocytes harvested from peripheral blood. Alternatively, CD34 positive cells harvested from peripheral blood, umbilical cord blood or bone marrow may be differentiated into dendritic cells by adding to the culture medium combinations of GM-CSF, IL-3, TNFα, CD40 ligand, LPS, flt3 ligand and/or other compound(s) that induce differentiation, maturation and proliferation of dendritic cells.

Dendritic cells are conveniently categorized as "immature" and "mature" cells, which allows a simple way to discriminate between two well characterized phenotypes. However, this nomenclature should not be construed to exclude all possible intermediate stages of differentiation. Immature dendritic cells are characterized as APC with a high capacity for antigen uptake and processing, which correlates with the high expression of Fcy receptor and mannose receptor. The mature phenotype is typically characterized by a lower expression of these markers, but a high expression of cell surface molecules responsible for T cell activation such as class I and class II MHC, adhesion molecules (e.g., CD54 and CD11) and costimulatory molecules (e.g., CD40, CD80, CD86 and 4-1BB).

APCs may generally be transfected with a polynucleotide encoding a lung tumor protein (or portion or other variant thereof) such that the lung tumor polypeptide, or an immunogenic portion thereof, is expressed on the cell surface. Such transfection may take place ex vivo, and a composition comprising such transfected cells may then be used for therapeutic purposes, as described herein. Alternatively, a gene delivery vehicle that targets a dendritic or other antigen presenting cell may be administered to a patient, resulting in transfection that occurs in vivo. In vivo and ex vivo transfection of dendritic cells, for example, may generally be performed using any methods known in the art, such as those described in WO 97/24447, or the gene gun approach described by Mahvi et al., Immunology and cell Biology 75:456-460, 1997. Antigen loading of dendritic cells may be achieved by incubating dendritic cells or progenitor cells with the lung tumor polypeptide, DNA (naked or within a plasmid vector) or RNA; or with antigen-expressing recombinant bacterium or viruses (e.g., vaccinia, fowlpox, adenovirus or lentivirus vectors). Prior to loading, the polypeptide may be covalently conjugated to an immunological partner that provides T cell help (e.g., a carrier molecule). Alternatively, a dendritic cell may be pulsed with a nonconjugated immunological partner, separately or in the presence of the polypeptide.

Immunogenic compositions and pharmaceutical compositions may be presented in unit-dose or multi-dose containers, such as sealed ampoules or vials. Such containers are preferably hermetically sealed to preserve sterility of the formulation until use. In general, formulations may be stored as suspensions, solutions or emulsions in oily or aqueous vehicles. Alternatively, an immunogenic or pharmaceutical composition may be stored in a freeze-dried condition requiring only the addition of a sterile liquid carrier immediately prior to use.

25 CANCER THERAPY

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In further aspects of the present invention, the compositions described herein may be used for immunotherapy of cancer, such as lung cancer. Within such methods, compositions are typically administered to a patient. As used herein, a "patient" refers to any warm-blooded animal, preferably a human. A patient may or may not be afflicted with cancer. Accordingly, the above pharmaceutical compositions

and immunogenic compositions may be used to prevent the development of a cancer or to treat a patient afflicted with a cancer. A cancer may be diagnosed using criteria generally accepted in the art, including the presence of a malignant tumor. Pharmaceutical compositions and immunogenic composition s may be administered either prior to or following surgical removal of primary tumors and/or treatment such as administration of radiotherapy or conventional chemotherapeutic drugs. Administration may be by any suitable method, including administration by intravenous, intraperitoneal, intramuscular, subcutaneous, intranasal, intradermal, anal, vaginal, topical and oral routes.

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Within certain embodiments, immunotherapy may be active immunotherapy, in which treatment relies on the *in vivo* stimulation of the endogenous host immune system to react against tumors with the administration of immune response-modifying agents (such as polypeptides and polynucleotides as provided herein).

Within other embodiments, immunotherapy passive may be immunotherapy, in which treatment involves the delivery of agents with established tumor-immune reactivity (such as effector cells or antibodies) that can directly or indirectly mediate antitumor effects and does not necessarily depend on an intact host immune system. Examples of effector cells include T cells as discussed above, T lymphocytes (such as CD8⁺ cytotoxic T lymphocytes and CD4⁺ T-helper tumorinfiltrating lymphocytes), killer cells (such as Natural Killer cells and lymphokineactivated killer cells), B cells and antigen-presenting cells (such as dendritic cells and macrophages) expressing a polypeptide provided herein. T cell receptors and antibody receptors specific for the polypeptides recited herein may be cloned, expressed and transferred into other vectors or effector cells for adoptive immunotherapy. polypeptides provided herein may also be used to generate antibodies or anti-idiotypic antibodies (as described above and in U.S. Patent No. 4,918,164) for passive immunotherapy.

Effector cells may generally be obtained in sufficient quantities for adoptive immunotherapy by growth *in vitro*, as described herein. Culture conditions for expanding single antigen-specific effector cells to several billion in number with

retention of antigen recognition in vivo are well known in the art. Such in vitro culture conditions typically use intermittent stimulation with antigen, often in the presence of cytokines (such as IL-2) and non-dividing feeder cells. As noted above, immunoreactive polypeptides as provided herein may be used to rapidly expand antigen-specific T cell cultures in order to generate a sufficient number of cells for immunotherapy. In particular, antigen-presenting cells, such as dendritic, macrophage, monocyte, fibroblast and/or B cells, may be pulsed with immunoreactive polypeptides or transfected with one or more polynucleotides using standard techniques well known For example, antigen-presenting cells can be transfected with a in the art. polynucleotide having a promoter appropriate for increasing expression in a recombinant virus or other expression system. Cultured effector cells for use in therapy must be able to grow and distribute widely, and to survive long term in vivo. Studies have shown that cultured effector cells can be induced to grow in vivo and to survive long term in substantial numbers by repeated stimulation with antigen supplemented with IL-2 (see, for example, Cheever et al., Immunological Reviews 157:177, 1997).

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Alternatively, a vector expressing a polypeptide recited herein may be introduced into antigen presenting cells taken from a patient and clonally propagated ex vivo for transplant back into the same patient. Transfected cells may be reintroduced into the patient using any means known in the art, preferably in sterile form by intravenous, intracavitary, intraperitoneal or intratumor administration.

Routes and frequency of administration of the therapeutic compositions described herein, as well as dosage, will vary from individual to individual, and may be readily established using standard techniques. In general, the pharmaceutical compositions and immunogenic compositions may be administered by injection (e.g., intracutaneous, intramuscular, intravenous or subcutaneous), intranasally (e.g., by aspiration) or orally. Preferably, between 1 and 10 doses may be administered over a 52 week period. Preferably, 6 doses are administered, at intervals of 1 month, and booster vaccinations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of a compound that, when administered as described above, is capable of promoting an anti-tumor immune response, and is at least 10-50% above the basal (i.e., untreated) level. Such response

can be monitored by measuring the anti-tumor antibodies in a patient or by vaccine-dependent generation of cytolytic effector cells capable of killing the patient's tumor cells *in vitro*. Such vaccines, or immunogenic compositions, should also be capable of causing an immune response that leads to an improved clinical outcome (e.g., more frequent remissions, complete or partial or longer disease-free survival) in vaccinated patients as compared to non-vaccinated patients. In general, for compositions comprising one or more polypeptides, the amount of each polypeptide present in a dose ranges from about 25 µg to 5 mg per kg of host. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.1 mL to about 5 mL.

In general, an appropriate dosage and treatment regimen provides the active compound(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit. Such a response can be monitored by establishing an improved clinical outcome (e.g., more frequent remissions, complete or partial, or longer disease-free survival) in treated patients as compared to non-treated patients. Increases in preexisting immune responses to a lung tumor protein generally correlate with an improved clinical outcome. Such immune responses may generally be evaluated using standard proliferation, cytotoxicity or cytokine assays, which may be performed using samples obtained from a patient before and after treatment.

CANCER DETECTION AND DIAGNOSIS

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In general, a cancer may be detected in a patient based on the presence of one or more lung tumor proteins and/or polynucleotides encoding such proteins in a biological sample (for example, blood, sera, sputum urine and/or tumor biopsies) obtained from the patient. In other words, such proteins may be used as markers to indicate the presence or absence of a cancer such as lung cancer. In addition, such proteins may be useful for the detection of other cancers. The binding agents provided herein generally permit detection of the level of antigen that binds to the agent in the biological sample. Polynucleotide primers and probes may be used to detect the level of mRNA encoding a tumor protein, which is also indicative of the presence or absence of a cancer. In general, a lung tumor sequence should be present at a level that is at least three fold higher in tumor tissue than in normal tissue

There are a variety of assay formats known to those of ordinary skill in the art for using a binding agent to detect polypeptide markers in a sample. See, e.g., Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988. In general, the presence or absence of a cancer in a patient may be determined by (a) contacting a biological sample obtained from a patient with a binding agent; (b) detecting in the sample a level of polypeptide that binds to the binding agent; and (c) comparing the level of polypeptide with a predetermined cut-off value.

In a preferred embodiment, the assay involves the use of binding agent immobilized on a solid support to bind to and remove the polypeptide from the remainder of the sample. The bound polypeptide may then be detected using a detection reagent that contains a reporter group and specifically binds to the binding agent/polypeptide complex. Such detection reagents may comprise, for example, a binding agent that specifically binds to the polypeptide or an antibody or other agent that specifically binds to the binding agent, such as an anti-immunoglobulin, protein G, protein A or a lectin. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding agent after incubation of the binding agent with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding agent is indicative of the reactivity of the sample with the immobilized binding agent. Suitable polypeptides for use within such assays include full length lung tumor proteins and portions thereof to which the binding agent binds, as described above.

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The solid support may be any material known to those of ordinary skill in the art to which the tumor protein may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption,

and covalent attachment (which may be a direct linkage between the agent and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for a suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of a plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about $10 \mu g$, and preferably about $100 \mu g$, as sufficient to immobilize an adequate amount of binding agent.

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Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (see, e.g., Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

In certain embodiments, the assay is a two-antibody sandwich assay. This assay may be performed by first contacting an antibody that has been immobilized on a solid support, commonly the well of a microtiter plate, with the sample, such that polypeptides within the sample are allowed to bind to the immobilized antibody. Unbound sample is then removed from the immobilized polypeptide-antibody complexes and a detection reagent (preferably a second antibody capable of binding to a different site on the polypeptide) containing a reporter group is added. The amount of detection reagent that remains bound to the solid support is then determined using a method appropriate for the specific reporter group.

More specifically, once the antibody is immobilized on the support as described above, the remaining protein binding sites on the support are typically blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or Tween 20TM (Sigma Chemical Co., St. Louis, MO). The

immobilized antibody is then incubated with the sample, and polypeptide is allowed to bind to the antibody. The sample may be diluted with a suitable diluent, such as phosphate-buffered saline (PBS) prior to incubation. In general, an appropriate contact time (i.e., incubation time) is a period of time that is sufficient to detect the presence of polypeptide within a sample obtained from an individual with lung cancer. Preferably, the contact time is sufficient to achieve a level of binding that is at least about 95% of that achieved at equilibrium between bound and unbound polypeptide. Those of ordinary skill in the art will recognize that the time necessary to achieve equilibrium may be readily determined by assaying the level of binding that occurs over a period of time. At room temperature, an incubation time of about 30 minutes is generally sufficient.

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Unbound sample may then be removed by washing the solid support with an appropriate buffer, such as PBS containing 0.1% Tween 20TM. The second antibody, which contains a reporter group, may then be added to the solid support. Preferred reporter groups include those groups recited above.

The detection reagent is then incubated with the immobilized antibody-polypeptide complex for an amount of time sufficient to detect the bound polypeptide. An appropriate amount of time may generally be determined by assaying the level of binding that occurs over a period of time. Unbound detection reagent is then removed and bound detection reagent is detected using the reporter group. The method employed for detecting the reporter group depends upon the nature of the reporter group. For radioactive groups, scintillation counting or autoradiographic methods are generally appropriate. Spectroscopic methods may be used to detect dyes, luminescent groups and fluorescent groups. Biotin may be detected using avidin, coupled to a different reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme reporter groups may generally be detected by the addition of substrate (generally for a specific period of time), followed by spectroscopic or other analysis of the reaction products.

To determine the presence or absence of a cancer, such as lung cancer, the signal detected from the reporter group that remains bound to the solid support is generally compared to a signal that corresponds to a predetermined cut-off value. In

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one preferred embodiment, the cut-off value for the detection of a cancer is the average mean signal obtained when the immobilized antibody is incubated with samples from patients without the cancer. In general, a sample generating a signal that is three standard deviations above the predetermined cut-off value is considered positive for the cancer. In an alternate preferred embodiment, the cut-off value is determined using a Receiver Operator Curve, according to the method of Sackett et al., Clinical Epidemiology: A Basic Science for Clinical Medicine, Little Brown and Co., 1985, p. 106-7. Briefly, in this embodiment, the cut-off value may be determined from a plot of pairs of true positive rates (i.e., sensitivity) and false positive rates (100%specificity) that correspond to each possible cut-off value for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (i.e., the value that encloses the largest area) is the most accurate cut-off value, and a sample generating a signal that is higher than the cut-off value determined by this method may be considered positive. Alternatively, the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, to minimize the false negative rate. In general, a sample generating a signal that is higher than the cut-off value determined by this method is considered positive for a cancer.

In a related embodiment, the assay is performed in a flow-through or strip test format, wherein the binding agent is immobilized on a membrane, such as nitrocellulose. In the flow-through test, polypeptides within the sample bind to the immobilized binding agent as the sample passes through the membrane. A second, labeled binding agent then binds to the binding agent-polypeptide complex as a solution containing the second binding agent flows through the membrane. The detection of bound second binding agent may then be performed as described above. In the strip test format, one end of the membrane to which binding agent is bound is immersed in a solution containing the sample. The sample migrates along the membrane through a region containing second binding agent and to the area of immobilized binding agent. Concentration of second binding agent at the area of immobilized antibody indicates the presence of a cancer. Typically, the concentration of second binding agent at that site generates a pattern, such as a line, that can be read visually. The absence of such a pattern indicates a negative result. In general, the amount of binding agent immobilized

on the membrane is selected to generate 'a visually discernible pattern when the biological sample contains a level of polypeptide that would be sufficient to generate a positive signal in the two-antibody sandwich assay, in the format discussed above. Preferred binding agents for use in such assays are antibodies and antigen-binding fragments thereof. Preferably, the amount of antibody immobilized on the membrane ranges from about 25 ng to about 1µg, and more preferably from about 50 ng to about 500 ng. Such tests can typically be performed with a very small amount of biological sample.

Of course, numerous other assay protocols exist that are suitable for use with the tumor proteins or binding agents of the present invention. The above descriptions are intended to be exemplary only. For example, it will be apparent to those of ordinary skill in the art that the above protocols may be readily modified to use lung tumor polypeptides to detect antibodies that bind to such polypeptides in a biological sample. The detection of such lung tumor protein specific antibodies may correlate with the presence of a cancer.

A cancer may also, or alternatively, be detected based on the presence of T cells that specifically react with a lung tumor protein in a biological sample. Within certain methods, a biological sample comprising CD4⁺ and/or CD8⁺ T cells isolated from a patient is incubated with a lung tumor polypeptide, a polynucleotide encoding such a polypeptide and/or an APC that expresses at least an immunogenic portion of such a polypeptide, and the presence or absence of specific activation of the T cells is detected. Suitable biological samples include, but are not limited to, isolated T cells. For example, T cells may be isolated from a patient by routine techniques (such as by Ficoll/Hypaque density gradient centrifugation of peripheral blood lymphocytes). T cells may be incubated *in vitro* for 2-9 days (typically 4 days) at 37°C with polypeptide (e.g., 5 - 25 μg/ml). It may be desirable to incubate another aliquot of a T cell sample in the absence of lung tumor polypeptide to serve as a control. For CD4⁺ T cells, activation is preferably detected by evaluating proliferation of the T cells. For CD8⁺ T cells, activation is preferably detected by evaluating cytolytic activity. A level of proliferation that is at least two fold greater and/or a level of cytolytic activity that is at

least 20% greater than in disease-free patients indicates the presence of a cancer in the patient.

As noted above, a cancer may also, or alternatively, be detected based on the level of mRNA encoding a lung tumor protein in a biological sample. For example, at least two oligonucleotide primers may be employed in a polymerase chain reaction (PCR) based assay to amplify a portion of a lung tumor cDNA derived from a biological sample, wherein at least one of the oligonucleotide primers is specific for (*i.e.*, hybridizes to) a polynucleotide encoding the lung tumor protein. The amplified cDNA is then separated and detected using techniques well known in the art, such as gel electrophoresis. Similarly, oligonucleotide probes that specifically hybridize to a polynucleotide encoding a lung tumor protein may be used in a hybridization assay to detect the presence of polynucleotide encoding the tumor protein in a biological sample.

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To permit hybridization under assay conditions, oligonucleotide primers and probes should comprise an oligonucleotide sequence that has at least about 60%, preferably at least about 75% and more preferably at least about 90%, identity to a portion of a polynucleotide encoding a lung tumor protein that is at least 10 nucleotides, and preferably at least 20 nucleotides, in length. Preferably, oligonucleotide primers and/or probes hybridize to a polynucleotide encoding a polypeptide described herein under moderately stringent conditions, as defined above. Oligonucleotide primers and/or probes which may be usefully employed in the diagnostic methods described herein preferably are at least 10-40 nucleotides in length. In a preferred embodiment, the oligonucleotide primers comprise at least 10 contiguous nucleotides, more preferably at least 15 contiguous nucleotides, of a DNA molecule having a sequence recited in SEQ ID NO: 1, 11-13, 15, 20, 23-27, 29, 30, 33, 34, 39, 41, 43-46, 51, 52, 57, 58, 60, 62, 65-67, 69-71, 74, 76, 79, 80, 84, 86, 89-92, 95, 97, 98, 101, 110, 111, 113-119, 121-128, 130-134, 136, 138, 139, 141, 143, 146-151, 153, 154, 157-160, 162-164, 167-178, 180, 181, 183, 186-190, 192, 193, 195-220, 224, 226-231, 234, 236, 237, 240, 241, 244-246, 248, 254, 255, 261, 262, 266, 270, 275, 280, 282, 283, 288, 289, 290, 292, 295, 301, 303, 304, 309, 311, 341-782, 784, 785, 790, 792, 794, 796, 800-804, 807, 808 or 810-826. Techniques for both PCR based assays and hybridization assays

are well known in the art (see, for example, Mullis et al., Cold Spring Harbor Symp. Quant. Biol., 51:263, 1987; Erlich ed., PCR Technology, Stockton Press, NY, 1989).

One preferred assay employs RT-PCR, in which PCR is applied in conjunction with reverse transcription. Typically, RNA is extracted from a biological sample, such as biopsy tissue, and is reverse transcribed to produce cDNA molecules. PCR amplification using at least one specific primer generates a cDNA molecule, which may be separated and visualized using, for example, gel electrophoresis. Amplification may be performed on biological samples taken from a test patient and from an individual who is not afflicted with a cancer. The amplification reaction may be performed on several dilutions of cDNA spanning two orders of magnitude. A two-fold or greater increase in expression in several dilutions of the test patient sample as compared to the same dilutions of the non-cancerous sample is typically considered positive.

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In another embodiment, the compositions described herein may be used as markers for the progression of cancer. In this embodiment, assays as described above for the diagnosis of a cancer may be performed over time, and the change in the level of reactive polypeptide(s) or polynucleotide(s) evaluated. For example, the assays may be performed every 24-72 hours for a period of 6 months to 1 year, and thereafter performed as needed. In general, a cancer is progressing in those patients in whom the level of polypeptide or polynucleotide detected increases over time. In contrast, the cancer is not progressing when the level of reactive polypeptide or polynucleotide either remains constant or decreases with time.

Certain *in vivo* diagnostic assays may be performed directly on a tumor. One such assay involves contacting tumor cells with a binding agent. The bound binding agent may then be detected directly or indirectly via a reporter group. Such binding agents may also be used in histological applications. Alternatively, polynucleotide probes may be used within such applications.

As noted above, to improve sensitivity, multiple lung tumor protein markers may be assayed within a given sample. It will be apparent that binding agents specific for different proteins provided herein may be combined within a single assay. Further, multiple primers or probes may be used concurrently. The selection of tumor

protein markers may be based on routine experiments to determine combinations that results in optimal sensitivity. In addition, or alternatively, assays for tumor proteins provided herein may be combined with assays for other known tumor antigens.

DIAGNOSTIC KITS

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The present invention further provides kits for use within any of the above diagnostic methods. Such kits typically comprise two or more components necessary for performing a diagnostic assay. Components may be compounds, reagents, containers and/or equipment. For example, one container within a kit may contain a monoclonal antibody or fragment thereof that specifically binds to a lung tumor protein. Such antibodies or fragments may be provided attached to a support material, as described above. One or more additional containers may enclose elements, such as reagents or buffers, to be used in the assay. Such kits may also, or alternatively, contain a detection reagent as described above that contains a reporter group suitable for direct or indirect detection of antibody binding.

Alternatively, a kit may be designed to detect the level of mRNA encoding a lung tumor protein in a biological sample. Such kits generally comprise at least one oligonucleotide probe or primer, as described above, that hybridizes to a polynucleotide encoding a lung tumor protein. Such an oligonucleotide may be used, for example, within a PCR or hybridization assay. Additional components that may be present within such kits include a second oligonucleotide and/or a diagnostic reagent or container to facilitate the detection of a polynucleotide encoding a lung tumor protein.

The following Examples are offered by way of illustration and not by way of limitation.

EXAMPLE 1

IDENTIFICATION AND CHARACTERIZATION OF LUNG TUMOR PROTEIN cDNAS

This Example illustrates the identification of cDNA molecules encoding lung tumor proteins.

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A. Isolation of cDNA Sequences from Lung Adenocarcinoma Libraries using Conventional cDNA Library Subtraction

A human lung adenocarcinoma cDNA expression library was constructed from poly A⁺ RNA from patient tissues (# 40031486) using a Superscript Plasmid System for cDNA Synthesis and Plasmid Cloning kit (BRL Life Technologies, Gaithersburg, MD) following the manufacturer's protocol. Specifically, lung carcinoma tissues were homogenized with polytron (Kinematica, Switzerland) and total RNA was extracted using Trizol reagent (BRL Life Technologies) as directed by the manufacturer. The poly A⁺ RNA was then purified using an oligo dT cellulose column as described in Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989. First-strand cDNA was synthesized using the NotI/Oligo-dT18 primer. Double-stranded cDNA was synthesized, ligated with BstXI/EcoRI adaptors (Invitrogen, San Diego, CA) and digested with Notl. Following size fractionation with cDNA size fractionation columns (BRL Life Technologies), the cDNA was ligated into the BstXI/NotI site of pcDNA3.1 (Invitrogen) and transformed into ElectroMax E. coli DH10B cells (BRL Life Technologies) by electroporation. A total of 3 x 10⁶ independent colonies were generated.

Using the same procedure, a normal human cDNA expression library was prepared from a panel of normal tissue specimens, including lung, liver, pancreas, skin, kidney, brain and resting PBMC.

cDNA library subtraction was performed using the above lung adenocarcinoma and normal tissue cDNA libraries, as described by Hara et al. (Blood, 84:189-199, 1994) with some modifications. Specifically, a lung adenocarcinoma-

specific subtracted cDNA library was generated as follows. The normal tissue cDNA library (80 μg) was digested with BamHI and XhoI, followed by a filling-in reaction with DNA polymerase Klenow fragment. After phenol-chloroform extraction and ethanol precipitation, the DNA was dissolved in 133 μl of H₂O, heat-denatured and mixed with 133 μl (133 μg) of Photoprobe biotin (Vector Laboratories, Burlingame, CA). As recommended by the manufacturer, the resulting mixture was irradiated with a 270 W sunlamp on ice for 20 minutes. Additional Photoprobe biotin (67 μl) was added and the biotinylation reaction was repeated. After extraction with butanol five times, the DNA was ethanol-precipitated and dissolved in 23 μl H₂O. The resulting DNA, plus other highly redundant cDNA clones that were frequently recovered in previous lung subtractions formed the driver DNA.

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To form the tracer DNA, 10 µg lung adenocarcinoma cDNA library was digested with NotI and SpeI, phenol chloroform extracted and passed through Chroma spin-400 columns (Clontech, Palo Alto, CA). Typically, 5 µg of cDNA was recovered after the sizing column. Following ethanol precipitation, the tracer DNA was dissolved in 5 µl H₂O. Tracer DNA was mixed with 15 µl driver DNA and 20 µl of 2 x hybridization buffer (1.5 M NaCl/10 mM EDTA/50 mM HEPES pH 7.5/0.2% sodium dodecyl sulfate), overlaid with mineral oil, and heat-denatured completely. The sample was immediately transferred into a 68 °C water bath and incubated for 20 hours (long The reaction mixture was then subjected to a streptavidin hybridization [LH]). treatment followed by phenol/chloroform extraction. This process was repeated three more times. Subtracted DNA was precipitated, dissolved in 12 µl H₂O, mixed with 8 µl driver DNA and 20 µl of 2 x hybridization buffer, and subjected to a hybridization at 68 ⁰C for 2 hours (short hybridization [SH]). After removal of biotinylated doublestranded DNA, subtracted cDNA was ligated into Notl/SpeI site of chloramphenicol resistant pBCSK+ (Stratagene, La Jolla, CA) and transformed into ElectroMax E. coli DH10B cells by electroporation to generate a lung adenocarcinoma specific subtracted cDNA library, referred to as LAT-S1 Similarly, LAT-S2 was generated by including 23 genes that were over-expressed in the tracer as additional drivers.

A second human lung adenocarcinoma cDNA expression library was constructed using adenocarcinoma tissue from a second patient (# 86-66) and used to

prepare a second lung adenocarcinoma-specific subtracted cDNA library (referred to as LAT2-S2), as described above, using the same panel of normal tissues and the additional genes over-expressed in LAT-S1.

A third human metastatic lung adenocarcinoma library was constructed from a pool of two lung pleural effusions with lung and gastric adenocarcinoma origins. The subtracted cDNA library, Mets-sub2 was generated as described above using the same panel of normal tissues. However, the Mets-sub3 subtracted library was constructed by including 51 additional genes as drivers. These 51 genes were recovered in Mets-sub2, representing over-expressed housekeeping genes in the testers. As a result, Mets-sub3 is more complexed and normalized.

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A total of 16 cDNA fragments isolated from LAT-S1, 585 cDNA fragments isolated from LAT-S2, 568 cDNA clones from LAT2-S2, 15 cDNA clones from Mets-sub2 and 343 cDNA clones from Mets-sub3, described above, were colony PCR amplified and their mRNA expression levels in lung tumor, normal lung, and various other normal and tumor tissues were determined using microarray technology (Incyte, Palo Alto, CA). Briefly, the PCR amplification products were dotted onto slides in an array format, with each product occupying a unique location in the array. mRNA was extracted from the tissue sample to be tested, reverse transcribed, and fluorescent-labeled cDNA probes were generated. The microarrays were probed with the labeled cDNA probes, the slides scanned and fluorescence intensity was measured. This intensity correlates with the hybridization intensity. Seventy-three non-redundant cDNA clones, of which 42 were found to be unique, showed over-expression in lung tumors, with expression in normal tissues tested (lung, skin, lymph node, colon, liver, pancreas, breast, heart, bone marrow, large intestine, kidney, stomach, brain, small intestine, bladder and salivary gland) being either undetectable, or at significantly lower levels compared to lung adenocarcinoma tumors. These clones were further characterized by DNA sequencing with a Perkin Elmer/Applied Biosystems Division Automated Sequencer Model 373A and/or Model 377 (Foster City, CA).

The sequences were compared to known sequences in the gene bank using the EMBL GenBank databases (release 96). No significant homologies were found to the sequence provided in SEQ ID NO: 67, with no apparent homology to

previously identified expressed sequence tags (ESTs). The sequences of SEQ ID NO: 60, 62, 65, 66, 69-71, 74, 76, 79, 80, 84, 86, 89-92, 95, 97 and 98 were found to show some homology to previously identified expressed sequence tags (ESTs). The cDNA sequences of SEQ ID NO: 59, 61, 63, 64, 67, 68, 72, 73, 75, 77, 78, 81-83, 85, 87, 88, 93, 94, 96, 99 and 100 showed homology to previously identified genes. The full-length cDNA sequences for the clones of SEQ ID NO: 96 and 100 are provided in SEQ ID NO: 316 and 318, respectively. The amino acid sequences for the clones of SEQ ID NO: 59, 61, 63, 64, 68, 73, 82, 83, 94, 96 and 100 are provided in SEQ ID NO: 331, 328, 329, 332, 327, 333, 330, 326, 325, 324 and 335, respectively. A predicted amino acid sequence encoded by the sequence of SEQ ID NO: 69 (referred to as L552S) is provided in SEQ ID NO: 786.

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Further studies led to the isolation of an extended cDNA sequence, and open reading frame, for L552S (SEQ ID NO: 790). The predicted amino acid sequence encoded by the cDNA sequence of SEQ ID NO: 790 is provided in SEQ ID NO: 791.

The determined cDNA sequence of an isoform of L552S is provided in SEQ ID NO: 792, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 793. Subsequent studies led to the isolation of the full-length cDNA sequence of L552S (SEQ ID NO: 808). The corresponding amino acid sequence is provided in SEQ ID NO: 809. No homologies were found to the protein sequence of L552S. However, nucleotides 533-769 of the full-length cDNA sequence were found to show homology to a previously identified DNA sequence.

Full-length cloning efforts on L552S led to the isolation of three additional cDNA sequences (SEQ ID NO: 810-812) from a metastatic lung adenocarcinoma library. The sequence of SEQ ID NO: 810 was found to show some homology to previously identified human DNA sequences. The sequence of SEQ ID NO: 811 was found to show some homology to a previously identified DNA sequence. The sequence of SEQ ID NO: 812 was found to show some homology to previously identified ESTs.

The gene of SEQ ID NO: 84 (referred to as L551S) was determined by real-time RT-PCR analysis to be over-expressed in 2/9 primary adenocarcinomas and to be expressed at lower levels in 2/2 metastatic adenocarcinomas and 1/2 squamous cell

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carcinomas. No expression was observed in normal tissues, with the exception of very low expression in normal stomach. Further studies on L551S led to the isolation of the 5' and 3' cDNA consensus sequences provided in SEQ ID NO: 801 and 802, respectively. The L551S 5' sequence was found to show some homology to the previously identified gene STY8 (cDNA sequence provided in SEQ ID NO: 803; corresponding amino acid sequence provided in SEQ ID NO: 805), which is a mitogen activated protein kinase phosphatase. However, no significant homologies were found to the 3' sequence of L551S. Subsequently, an extended cDNA sequence for L551S was isolated (SEQ ID NO: 804). The corresponding amino acid sequence is provided in SEO ID NO: 806. Further studies led to the isolation of two independent full-length clones for L551S (referred to as 54298 and 54305). These two clones have five nucleotide differences compared to the STY8 DNA sequence. Two of these differences are single nucleotide polymorphisms which do not effect the encoded amino acid sequences. The other three nucleotide differences are consistent between the two L551S clones but lead to encoded amino acid sequences that are different from the STY8 protein sequence. The determined cDNA sequences for the L551S full-length clones 54305 and 54298 are provided in SEQ ID NO: 825 and 826, respectively, with the amino acid sequence for L551S being provided in SEQ ID NO: 827.

B. Isolation of cDNA Sequences from Lung Adenocarcinoma Libraries using PCR-Based cDNA Library Subtraction

cDNA clones from a PCR-based subtraction library, containing cDNA from a pool of two human lung primary adenocarcinomas subtracted against a pool of nine normal human tissue cDNAs including skin, colon, lung, esophagus, brain, kidney, spleen, pancreas and liver, (Clontech, Palo Alto, CA) were derived and submitted to a first round of PCR amplification. This library (referred to as ALT-1) was subjected to a second round of PCR amplification, following the manufacturer's protocol. The expression levels of 760 cDNA clones in lung tumor, normal lung, and various other normal and tumor tissues, were examined using microarray technology as described above. A total of 118 clones, of which 55 were unique, were found to be overexpressed in lung tumor tissue, with expression in normal tissues tested (lung, skin,

lymph node, colon, liver, pancreas, breast, heart, bone marrow, large intestine, kidney, stomach, brain, small intestine, bladder and salivary gland) being either undetectable, or at significantly lower levels. The sequences were compared to known sequences in the gene bank using the EMBL and GenBank databases (release 96). No significant homologies (including ESTs) were found to the sequence provided in SEQ ID NO: 44. The sequences of SEQ ID NO: 1, 11, 13, 15, 20, 23-27, 29, 30, 33, 34, 39, 41, 43, 45, 46, 51 and 57 were found to show some homology to previously identified expressed sequence tags (ESTs). The cDNA sequences of SEQ ID NO: 2-10, 12, 14, 16-19, 21, 22, 28, 31, 32, 35-38, 40, 42, 44, 47-50, 52-56 and 58 showed homology to previously identified genes. The full-length cDNA sequences for the clones of SEQ ID NO: 18, 22, 31, 35, 36 and 42 are provided in SEQ ID NO: 320, 319, 323, 321, 317, 321 and 322, respectively, with the corresponding amino acid sequences being provided in SEQ ID NO: 337, 336, 340, 338, 334, and 339, respectively.

Further studies led to the isolation of an extended cDNA sequence for the clone of SEQ ID NO: 33 (referred to as L801P). This extended cDNA sequence (provided in SEQ ID NO: 796), was found to contain three potential open reading frames (ORFs). The predicted amino acid sequences encoded by these three ORFs are provided in SEQ ID NO: 797-799, respectively.

In subsequent studies, a full-length cDNA sequence for the clone of SEQ ID NO: 44 (referred to as L844P) was isolated (provided in SEQ ID NO: 800). Comparison of this sequence with those in the public databases revealed that the 470 bases at the 5' end of the sequence show homology to the known gene dihydrodiol dehydrogenase, thus indicating that L844P is a novel transcript of the dihydrodiol dehydrogenase family having 2007 base pairs of previously unidentified 3' untranslated region.

The predicted amino acid sequence encoded by the sequence of SEQ ID NO: 46 (referred to as L840P) is provided in SEQ ID NO: 787. An extended cDNA sequence for L840P, which was determined to include an open reading frame, is provided in SEQ ID NO: 794. The predicted amino acid sequence encoded by the cDNA sequence of SEQ ID NO: 794 is provided in SEQ ID NO: 795. The full-length cDNA sequence for the clone of SEQ ID NO: 54 (referred to as L548S) is provided in

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SEQ ID NO: 788, with the corresponding amino acid sequence being provided in SEQ ID NO: 789.

Northern blot analyses of the genes of SEQ ID NO: 25 and 46 (referred to as L839P and L840P, respectively) were remarkably similar. Both genes were expressed in 1/2 lung adenocarcinomas as two bands of 3.6 kb and 1.6 kb. No expression of L839P was observed in normal lung or trachea. No expression of L840P was observed in normal bone marrow, resting or activated PBMC, esophagus, or normal lung. Given the similar expression patterns, L839P and L840P may be derived from the same gene.

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Further studies on L773P (SEQ ID NO: 58) resulted in the isolation of the extended consensus cDNA sequence provided in SEQ ID NO: 807.

Additional lung adenocarcinoma cDNA clones were isolated as follows. A cDNA library was prepared from a pool of two lung adenocarcinomas and subtracted against cDNA from a panel of normal tissues including lung, brain, liver, kidney, pancreas, skin, heart and spleen. The subtraction was performed using a PCR-based protocol (Clontech), which was modified to generate larger fragments. Within this protocol, tester and driver double stranded cDNA were separately digested with five restriction enzymes that recognize six-nucleotide restriction sites (MluI, MscI, PvuII, Sall and Stul). This digestion resulted in an average cDNA size of 600 bp, rather than the average size of 300 bp that results from digestion with RsaI according to the Clontech protocol. The ends of the restriction digested tester cDNA were filled in to generate blunt ends for adapter ligation. This modification did not affect the subtraction efficiency. Two tester populations were then created with different adapters, and the driver library remained without adapters. The tester and driver libraries were then hybridized using excess driver cDNA. In the first hybridization step, driver was separately hybridized with each of the two tester cDNA populations. This resulted in populations of (a) unhybridized tester cDNAs, (b) tester cDNAs hybridized to other tester cDNAs, (c) tester cDNAs hybridized to driver cDNAs and (d) unhybridized driver cDNAs. The two separate hybridization reactions were then combined, and rehybridized in the presence of additional denatured driver cDNA. Following this second hybridization, in addition to populations (a) through (d), a fifth population (e)

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was generated in which tester cDNA with one adapter hybridized to tester cDNA with the second adapter. Accordingly, the second hybridization step resulted in enrichment of differentially expressed sequences which could be used as templates for PCR amplification with adaptor-specific primers.

The ends were then filled in, and PCR amplification was performed using adaptor-specific primers. Only population (e), which contained tester cDNA that did not hybridize to driver cDNA, was amplified exponentially. A second PCR amplification step was then performed, to reduce background and further enrich differentially expressed sequences.

Fifty-seven cDNA clones were isolated from the subtracted library (referred to as LAP1) and sequenced. The determined cDNA sequences for 16 of these clones are provided in SEQ ID NO: 101-116. The sequences of SEQ ID NO: 101 and 114 showed no significant homologies to previously identified sequences. The sequences of SEQ ID NO: 102-109 and 112 showed some similarity to previously identified sequences, while the sequences of SEQ ID NO: 113, 115 and 116 showed some similarity to previously isolated ESTs.

C. Isolation of cDNA Sequences from Small Cell Lung Carcinoma Libraries using PCR-Based cDNA Library Subtraction

A subtracted cDNA library for small cell lung carcinoma (referred to as SCL1) was prepared using essentially the modified PCR-based subtraction process described above. cDNA from small cell lung carcinoma was subtracted against cDNA from a panel of normal tissues, including normal lung, brain, kidney, liver, pancreas, skin, heart, lymph node and spleen. Both tester and driver poly A+ RNA were initially amplified using SMART PCR cDNA synthesis kit (Clontech, Palo Alto, CA). The tester and driver double stranded cDNA were separately digested with five restriction enzymes (DraI, MscI, PvuII, SmaI, and StuI). These restriction enzymes generated blunt end cuts and the digestion resulted in an average insert size of 600 bp. Digestion with this set of restriction enzymes eliminates the step required to generate blunt ends by filling in of the cDNA ends. These modifications did not affect subtraction efficiency.

Eighty-five clones were isolated and sequenced. The determined cDNA sequences for 31 of these clones are provided in SEQ ID NO: 117-147. The sequences of SEQ ID NO: 122, 124, 126, 127, 130, 131, 133, 136, 139 and 147 showed no significant homologies to previously identified sequences. The sequences of SEQ ID NO: 120, 129, 135, 137, 140, 142, 144 and 145 showed some similarity to previously identified gene sequences, while the sequences of SEQ ID NO: 114, 118, 119, 121, 123, 125, 128, 132, 134, 138, 141, 143 and 147 showed some similarity to previously isolated ESTs.

In further studies, three additional cDNA libraries were generated from poly A+ RNA from a single small cell lung carcinoma sample subtracted against a pool of poly A+ RNA from nine normal tissues (lung, brain, kidney, liver, pancreas, skin, heart pituitary gland and spleen). For the first library (referred to as SCL2), the subtraction was carried out essentially as described above for the LAP1 library, with the exception that the tester and driver were digested with PvuII, StuI, MscI and DraI. The ratio of tester and driver cDNA used was as recommended by Clontech. For the second library (referred to as SCL3), subtraction was performed essentially as for SCL2 except that cDNA for highly redundant clones identified from the SCL2 library was included in the driver cDNA. Construction of the SCL4 library was performed essentially as described for the SCL3 library except that a higher ratio of driver to tester was employed.

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Each library was characterized by DNA sequencing and database analyses. The determined cDNA sequence for 35 clones isolated from the SCL2 library are provided in SEQ ID NO: 245-279, with the determined cDNA sequences for 21 clones isolated from the SCL3 library and for 15 clones isolated from the SCL4 library being provided in SEQ ID NO: 280-300 and 301-315, respectively. The sequences of SEQ ID NO: 246, 254, 261, 262, 304, 309 and 311 showed no significant homologies to previously identified sequences. The sequence of SEQ ID NO: 245, 248, 255, 266, 270, 275, 280, 282, 283, 288-290, 292, 295, 301 and 303 showed some homology to previously isolated ESTs, while the sequences of SEQ ID NO: 247, 249-253, 256-260, 263-265, 267-269, 271-274, 276-279, 281, 284-287, 291, 293, 294, 296-300, 302, 305-308, 310 and 312-315 showed some homology to previously identified gene sequences.

D. Isolation of cDNA Sequences from a Neuroendocrine Library using PCR-Based cDNA Library Subtraction

Using the modified PCR-based subtraction process, essentially as described above for the LAP1 subtracted library, a subtracted cDNA library (referred to as MLN1) was derived from a lung neuroendocrine carcinoma that had metastasized to the subcarinal lymph node, by subtraction with a panel of nine normal tissues, including normal lung, brain, kidney, liver, pancreas, skin, heart, lymph node and spleen.

Ninety-one individual clones were isolated and sequenced. The determined cDNA sequences for 58 of these clones are provided in SEQ ID NO: 147-222. The sequences of SEQ ID NO: 150, 151, 154, 157, 158, 159, 160, 163, 174, 175, 178, 186-190, 192, 193, 195-200, 208-210, 212-215 and 220 showed no significant homologies to previously identified sequences. The sequences of SEQ ID NO: 152, 155, 156, 161, 165, 166, 176, 179, 182, 184, 185, 191, 194, 221 and 222 showed some similarity to previously identified gene sequences, while the sequences of SEQ ID NO: 148, 149, 153, 164, 167-173, 177, 180, 181, 183, 201-207, 211 and 216-219 showed some similarity to previously isolated ESTs.

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The determined cDNA sequences of an additional 442 clones isolated from the MLN1 library are provided in SEQ ID NO: 341-782.

E. Isolation of cDNA Sequences from a Squamous Cell Lung Carcinoma Library using PCR-Based cDNA Library Subtraction

A subtracted cDNA library for squamous cell lung carcinoma (referred to as SQL1) was prepared, essentially using the modified PCR-based subtraction process described above, except the tester and driver double stranded cDNA were separately digested with four restriction enzymes (DraI, MscI, PvuII and StuI) cDNA from a pool of two squamous cell lung carcinomas was subtracted against cDNA from a pool of 10 normal tissues, including normal lung, brain, kidney, liver, pancreas, skin, heart, spleen, esophagus and trachea.

Seventy-four clones were isolated and sequenced. The determined cDNA sequences for 22 of these clones are provided in SEQ ID NO: 223-244. The sequence of SEQ ID NO: 241 showed no significant homologies to previously

identified sequences. The sequences of SEQ ID NO: 223, 225, 232, 233, 235, 238, 239, 242 and 243 showed some similarity to previously identified gene sequences, while the sequences of SEQ ID NO: 224, 226-231, 234, 236, 237, 240, 241 and 244 showed some similarity to previously isolated ESTs.

The sequences of an additional 12 clones isolated during chracterization of cDNA libraries prepared from lung tumor tissue are provided in SEQ ID NO: 813-824. Comparison of these sequences with those in the GenBank database and the GeneSeq DNA database revealed no significant homologies to previously identified sequences.

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EXAMPLE 2 SYNTHESIS OF POLYPEPTIDES

Polypeptides may be synthesized on a Perkin Elmer/Applied Biosystems Division 430A peptide synthesizer using FMOC chemistry with HPTU (O-15 Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate) activation. A Gly-Cys-Gly sequence may be attached to the amino terminus of the peptide to provide a method of conjugation, binding to an immobilized surface, or labeling of the peptide. Cleavage of the peptides from the solid support may be carried out using the following acid:ethanedithiol:thioanisole:water:phenol trifluoroacetic cleavage mixture: 20 (40:1:2:2:3). After cleaving for 2 hours, the peptides may be precipitated in cold methyl-t-butyl-ether. The peptide pellets may then be dissolved in water containing 0.1% trifluoroacetic acid (TFA) and lyophilized prior to purification by C18 reverse phase HPLC. A gradient of 0%-60% acetonitrile (containing 0.1% TFA) in water (containing 0.1% TFA) may be used to elute the peptides. Following lyophilization of 25 the pure fractions, the peptides may be characterized using electrospray or other types of mass spectrometry and by amino acid analysis.

EXAMPLE 3

PREPARATION OF ANTIBODIES AGAINST LUNG CANCER ANTIGENS

Polyclonal antibodies against the lung cancer antigen L773P (SEQ ID 5 NO: 783) were prepared as follows.

Rabbits were immunized with recombinant protein expressed in and purified from *E. coli* as described above. For the initial immunization, 400 µg of antigen combined with muramyl dipeptide (MDP) was injected subcutaneously (S.C.). Animals were boosted S.C. 4 weeks later with 200 µg of antigen mixed with incomplete Freund's Adjuvant (IFA). Subsequent boosts of 100 µg of antigen mixed with IFA were injected S.C. as necessary to induce high antibody titer responses. Serum bleeds from immunized rabbits were tested for L773P-specific reactivity using ELISA assays with purified protein and showed strong reactivity to L733P. Polyclonal antibodies against L773P were affinity purified from high titer polyclonal sera using purified protein attached to a solid support.

EXAMPLE 4

PROTEIN EXPRESSION OF LUNG TUMOR-SPECIFIC ANTIGENS

Full-length L773P (amino acids 2-364 of SEQ ID NO: 783), with a 6X His Tag, were subcloned into the pPDM expression vector and transformed into either BL21 CodonPlus or BL21 pLysS host cells using standard techniques. High levels of expression were observed in both cases. Similarly, the N-terminal portion of L773P (amino acids 2-71 of SEQ ID NO: 783; referred to as L773PA), with a 6X His tag were subcloned into the vector pPDM and transformed into BL21 CodonPlus host cells. Low levels of expression were observed by N-terminal sequencing. The sequence of the expressed constructs for L773P and L773PA are provided in SEQ ID NO: 784 and 785, respectively.

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From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

CLAIMS

What is claimed:

- 1. An isolated polypeptide, comprising at least an immunogenic portion of a lung tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:
- (a) sequences recited in SEQ ID NOs: 1, 11-13, 15, 20, 23-27, 29, 30, 33, 34, 39, 41, 43-46, 51, 52, 57, 58, 60, 62, 65-67, 69-71, 74, 76, 79, 80, 84, 86, 89-92, 95, 97, 98, 101, 110, 111, 113-119, 121-128, 130-134, 136, 138, 139, 141, 143, 146-151, 153, 154, 157-160, 162-164, 167-178, 180, 181, 183, 186-190, 192, 193, 195-220, 224, 226-231, 234, 236, 237, 240, 241, 244-246, 248, 254, 255, 261, 262, 266, 270, 275, 280, 282, 283, 288, 289, 290, 292, 295, 301, 303, 304, 309, 311, 341-782, 784, 785, 790, 792, 794, 796, 800, 802, 804, 807, 808 and 811-826;
- (b) sequences that hybridize to a sequence recited in any one of SEQ ID NOs: 1, 11-13, 15, 20, 23-27, 29, 30, 33, 34, 39, 41, 43-46, 51, 52, 57, 58, 60, 62, 65-67, 69-71, 74, 76, 79, 80, 84, 86, 89-92, 95, 97, 98, 101, 110, 111, 113-119, 121-128, 130-134, 136, 138, 139, 141, 143, 146-151, 153, 154, 157-160, 162-164, 167-178, 180, 181, 183, 186-190, 192, 193, 195-220, 224, 226-231, 234, 236, 237, 240, 241, 244-246, 248, 254, 255, 261, 262, 266, 270, 275, 280, 282, 283, 288, 289, 290, 292, 295, 301, 303, 304, 309, 311, 341-782, 784, 785, 790, 792, 794, 796, 800, 802, 804, 807, 808 and 811-826 under moderately stringent conditions; and
 - (c) complements of sequences of (a) or (b).
- 2. An isolated polypeptide according to claim 1, wherein the polypeptide comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs: 1, 11-13, 15, 20, 23-27, 29, 30, 33, 34, 39, 41, 43-46, 51, 52, 57, 58, 60, 62, 65-67, 69-71, 74, 76, 79, 80, 84, 86, 89-92, 95, 97, 98, 101, 110, 111, 113-119, 121-128, 130-134, 136, 138, 139, 141, 143, 146-151, 153, 154, 157-160, 162-164, 167-178, 180, 181, 183, 186-190, 192, 193, 195-220, 224, 226-231, 234, 236, 237, 240, 241, 244-246, 248, 254, 255, 261, 262, 266, 270, 275, 280, 282, 283, 288, 289, 290, 292, 295, 301, 303, 304, 309, 311, 341-

782, 784, 785, 790, 792, 794, 796, 800, 802, 804, 807, 808 and 811-826 or a complement of any of the foregoing polynucleotide sequences.

- 3. An isolated polypeptide comprising a sequence recited in any one of SEQ ID NOs: 786, 787, 791, 793, 795, 797-799, 806, 809 and 827.
- 4. An isolated polynucleotide encoding at least 15 amino acid residues of a lung tumor protein, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with antigen-specific antisera is not substantially diminished, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide comprising a sequence recited in any one of SEQ ID NO: 1, 11-13, 15, 20, 23-27, 29, 30, 33, 34, 39, 41, 43-46, 51, 52, 57, 58, 60, 62, 65-67, 69-71, 74, 76, 79, 80, 84, 86, 89-92, 95, 97, 98, 101, 110, 111, 113-119, 121-128, 130-134, 136, 138, 139, 141, 143, 146-151, 153, 154, 157-160, 162-164, 167-178, 180, 181, 183, 186-190, 192, 193, 195-220, 224, 226-231, 234, 236, 237, 240, 241, 244-246, 248, 254, 255, 261, 262, 266, 270, 275, 280, 282, 283, 288, 289, 290, 292, 295, 301, 303, 304, 309, 311, 341-782, 784, 785, 790, 792, 794, 796, 800, 802, 804, 807, 808 and 811-826, or a complement of any of the foregoing sequences.
- 5. An isolated polynucleotide encoding a lung tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide comprising a sequence recited in any one of SEQ ID NOs: 1, 11-13, 15, 20, 23-27, 29, 30, 33, 34, 39, 41, 43-46, 51, 52, 57, 58, 60, 62, 65-67, 69-71, 74, 76, 79, 80, 84, 86, 89-92, 95, 97, 98, 101, 110, 111, 113-119, 121-128, 130-134, 136, 138, 139, 141, 143, 146-151, 153, 154, 157-160, 162-164, 167-178, 180, 181, 183, 186-190, 192, 193, 195-220, 224, 226-231, 234, 236, 237, 240, 241, 244-246, 248, 254, 255, 261, 262, 266, 270, 275, 280, 282, 283, 288, 289, 290, 292, 295, 301, 303, 304, 309, 311, 341-782, 784, 785, 790, 792, 794, 796, 800, 802, 804, 807, 808 and 811-826 or a complement of any of the foregoing sequences.

6. An isolated polynucleotide, comprising a sequence recited in any one of SEQ ID NOs: 1, 11-13, 15, 20, 23-27, 29, 30, 33, 34, 39, 41, 43-46, 51, 52, 57, 58, 60, 62, 65-67, 69-71, 74, 76, 79, 80, 84, 86, 89-92, 95, 97, 98, 101, 110, 111, 113-119, 121-128, 130-134, 136, 138, 139, 141, 143, 146-151, 153, 154, 157-160, 162-164, 167-178, 180, 181, 183, 186-190, 192, 193, 195-220, 224, 226-231, 234, 236, 237, 240, 241, 244-246, 248, 254, 255, 261, 262, 266, 270, 275, 280, 282, 283, 288, 289, 290, 292, 295, 301, 303, 304, 309, 311, 341-782, 784, 785, 790, 792, 794, 796, 800, 802, 804, 807, 808 and 811-826.

- 7. An isolated polynucleotide, comprising a sequence that hybridizes to a sequence recited in any one of SEQ ID NOs: 1, 11-13, 15, 20, 23-27, 29, 30, 33, 34, 39, 41, 43-46, 51, 52, 57, 58, 60, 62, 65-67, 69-71, 74, 76, 79, 80, 84, 86, 89-92, 95, 97, 98, 101, 110, 111, 113-119, 121-128, 130-134, 136, 138, 139, 141, 143, 146-151, 153, 154, 157-160, 162-164, 167-178, 180, 181, 183, 186-190, 192, 193, 195-220, 224, 226-231, 234, 236, 237, 240, 241, 244-246, 248, 254, 255, 261, 262, 266, 270, 275, 280, 282, 283, 288, 289, 290, 292, 295, 301, 303, 304, 309, 311, 341-782, 784, 785, 790, 792, 794, 796, 800, 802, 804, 807, 808 and 811-826 under moderately stringent conditions.
- 8. An isolated polynucleotide complementary to a polynucleotide according to any one of claims 4-7.
- 9. An expression vector, comprising a polynucleotide according to any one of claims 4-8.
- 10. A host cell transformed or transfected with an expression vector according to claim 9.
- 11. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to a lung tumor protein that comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs: 1, 11-13, 15, 20, 23-27, 29, 30,

33, 34, 39, 41, 43-46, 51, 52, 57, 58, 60, 62, 65-67, 69-71, 74, 76, 79, 80, 84, 86, 89-92, 95, 97, 98, 101, 110, 111, 113-119, 121-128, 130-134, 136, 138, 139, 141, 143, 146-151, 153, 154, 157-160, 162-164, 167-178, 180, 181, 183, 186-190, 192, 193, 195-220, 224, 226-231, 234, 236, 237, 240, 241, 244-246, 248, 254, 255, 261, 262, 266, 270, 275, 280, 282, 283, 288, 289, 290, 292, 295, 301, 303, 304, 309, 311, 341-782, 784, 785, 790, 792, 794, 796, 800, 802, 804, 807, 808 and 811-826 or a complement of any of the foregoing polynucleotide sequences.

- 12. A fusion protein, comprising at least one polypeptide according to claim 1.
- 13. A fusion protein according to claim 12, wherein the fusion protein comprises an expression enhancer that increases expression of the fusion protein in a host cell transfected with a polynucleotide encoding the fusion protein.
- 14. A fusion protein according to claim 12, wherein the fusion protein comprises a T helper epitope that is not present within the polypeptide of claim 1.
- 15. A fusion protein according to claim 12, wherein the fusion protein comprises an affinity tag.
- 16. An isolated polynucleotide encoding a fusion protein according to claim 12.
- 17. A pharmaceutical composition, comprising a physiologically acceptable carrier and at least one component selected from the group consisting of:
 - (a) a polypeptide according to claim 1;
 - (b) a polynucleotide according to claim 4;
 - (c) an antibody according to claim 11;
 - (d) a fusion protein according to claim 12; and
 - (e) a polynucleotide according to claim 16.

18. An immunogenic composition comprising an immunostimulant and at least one component selected from the group consisting of:

- (a) a polypeptide according to claim 1;
- (b) a polynucleotide according to claim 4;
- (c) an antibody according to claim 11;
- (d) a fusion protein according to claim 12; and
- (e) a polynucleotide according to claim 16.
- 19. An immunogenic composition according to claim 18, wherein the immunostimulant is an adjuvant.
- 20. An immunogenic composition according to any claim 18, wherein the immunostimulant induces a predominantly Type I response.
- 21. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a pharmaceutical composition according to claim 17.
- 22. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of an immunogenic composition according to claim 18.
- 23. A pharmaceutical composition comprising an antigen-presenting cell that expresses a polypeptide according to claim 1, in combination with a pharmaceutically acceptable carrier or excipient.
- 24. A pharmaceutical composition according to claim 23, wherein the antigen presenting cell is a dendritic cell or a macrophage.

25. An immunogenic composition comprising an antigen-presenting cell that expresses a polypeptide comprising at least an immunogenic portion of a lung tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

- (a) sequences recited in SEQ ID NOs: 1, 11-13, 15, 20, 23-27, 29, 30, 33, 34, 39, 41, 43-46, 51, 52, 57, 58, 60, 62, 65-67, 69-71, 74, 76, 79, 80, 84, 86, 89-92, 95, 97, 98, 101, 110, 111, 113-119, 121-128, 130-134, 136, 138, 139, 141, 143, 146-151, 153, 154, 157-160, 162-164, 167-178, 180, 181, 183, 186-190, 192, 193, 195-220, 224, 226-231, 234, 236, 237, 240, 241, 244-246, 248, 254, 255, 261, 262, 266, 270, 275, 280, 282, 283, 288, 289, 290, 292, 295, 301, 303, 304, 309, 311, 341-782, 784, 785, 790, 792, 794, 796, 800-804, 807, 808 and 810-826;
- (b) sequences that hybridize to a sequence recited in any one of SEQ ID NOs: 1, 11-13, 15, 20, 23-27, 29, 30, 33, 34, 39, 41, 43-46, 51, 52, 57, 58, 60, 62, 65-67, 69-71, 74, 76, 79, 80, 84, 86, 89-92, 95, 97, 98, 101, 110, 111, 113-119, 121-128, 130-134, 136, 138, 139, 141, 143, 146-151, 153, 154, 157-160, 162-164, 167-178, 180, 181, 183, 186-190, 192, 193, 195-220, 224, 226-231, 234, 236, 237, 240, 241, 244-246, 248, 254, 255, 261, 262, 266, 270, 275, 280, 282, 283, 288, 289, 290, 292, 295, 301, 303, 304, 309, 311, 341-782, 784, 785, 790, 792, 794, 796, 800-804, 807, 808 and 810-826 under moderately stringent conditions; and
 - (c) complements of sequences of (i) or (ii); in combination with an immunostimulant.
- 26. An immunogenic composition according to claim 25, wherein the immunostimulant is an adjuvant.
- 27. An immunogenic composition according to claim 25, wherein the immunostimulant induces a predominantly Type I response.
- 28. An immunogenic composition according to claim 25, wherein the antigenpresenting cell is a dendritic cell.

29. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of an antigen-presenting cell that expresses a polypeptide comprising at least an immunogenic portion of a lung tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

- (a) sequences recited in SEQ ID NOs: 1, 11-13, 15, 20, 23-27, 29, 30, 33, 34, 39, 41, 43-46, 51, 52, 57, 58, 60, 62, 65-67, 69-71, 74, 76, 79, 80, 84, 86, 89-92, 95, 97, 98, 101, 110, 111, 113-119, 121-128, 130-134, 136, 138, 139, 141, 143, 146-151, 153, 154, 157-160, 162-164, 167-178, 180, 181, 183, 186-190, 192, 193, 195-220, 224, 226-231, 234, 236, 237, 240, 241, 244-246, 248, 254, 255, 261, 262, 266, 270, 275, 280, 282, 283, 288, 289, 290, 292, 295, 301, 303, 304, 309, 311, 341-782, 784, 785, 790, 792, 794, 796, 800-804, 807, 808 and 810-826;
- (b) sequences that hybridize to a sequence recited in any one of SEQ ID NOs: 1, 11-13, 15, 20, 23-27, 29, 30, 33, 34, 39, 41, 43-46, 51, 52, 57, 58, 60, 62, 65-67, 69-71, 74, 76, 79, 80, 84, 86, 89-92, 95, 97, 98, 101, 110, 111, 113-119, 121-128, 130-134, 136, 138, 139, 141, 143, 146-151, 153, 154, 157-160, 162-164, 167-178, 180, 181, 183, 186-190, 192, 193, 195-220, 224, 226-231, 234, 236, 237, 240, 241, 244-246, 248, 254, 255, 261, 262, 266, 270, 275, 280, 282, 283, 288, 289, 290, 292, 295, 301, 303, 304, 309, 311, 341-782, 784, 785, 790, 792, 794, 796, 800-804, 807, 808 and 810-826 under moderately stringent conditions; and
- (c) complements of sequences of (i) or (ii)encoded by a polynucleotide recited in any one of SEQ ID NOs: 1, 11-13, 15, 20, 23-27, 29, 30, 33, 34, 39, 41, 43-46, 51, 52, 57, 58, 60, 62, 65-67, 69-71, 74, 76, 79, 80, 84, 86, 89-92, 95, 97, 98, 101, 110, 111, 113-119, 121-128, 130-134, 136, 138, 139, 141, 143, 146-151, 153, 154, 157-160, 162-164, 167-178, 180, 181, 183, 186-190, 192, 193, 195-220, 224, 226-231, 234, 236, 237, 240, 241, 244-246, 248, 254, 255, 261, 262, 266, 270, 275, 280, 282, 283, 288, 289, 290, 292, 295, 301, 303, 304, 309, 311, 341-782, 784, 785, 790, 792, 794, 796, 800-804, 807, 808 and 810-826;

and thereby inhibiting the development of a cancer in the patient.

30. A method according to claim 29, wherein the antigen-presenting cell is a dendritic cell.

31. A method according to any one of claims 21, 22 and 29, wherein the cancer is lung cancer.

- 32. A method for removing tumor cells from a biological sample, comprising contacting a biological sample with T cells that specifically react with a lung tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:
- (i) polynucleotides recited in any one of SEQ ID NOs: 1, 11-13, 15, 20, 23-27, 29, 30, 33, 34, 39, 41, 43-46, 51, 52, 57, 58, 60, 62, 65-67, 69-71, 74, 76, 79, 80, 84, 86, 89-92, 95, 97, 98, 101, 110, 111, 113-119, 121-128, 130-134, 136, 138, 139, 141, 143, 146-151, 153, 154, 157-160, 162-164, 167-178, 180, 181, 183, 186-190, 192, 193, 195-220, 224, 226-231, 234, 236, 237, 240, 241, 244-246, 248, 254, 255, 261, 262, 266, 270, 275, 280, 282, 283, 289, 290, 292, 295, 301, 303, 304, 309, 311, 341-782, 784, 785, 790, 792, 794, 796, 800-804, 807, 808 and 810-826; and
 - (ii) complements of the foregoing polynucleotides;

wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the antigen from the sample.

- 33. A method according to claim 32, wherein the biological sample is blood or a fraction thereof.
- 34. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient a biological sample treated according to the method of claim 32.
- 35. A method for stimulating and/or expanding T cells specific for a lung tumor protein, comprising contacting T cells with at least one component selected from the group consisting of:

(a) polypeptides comprising at least an immunogenic portion of a lung tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

- (i) sequences recited in SEQ ID NOs: 1, 11-13, 15, 20, 23-27, 29, 30, 33, 34, 39, 41, 43-46, 51, 52, 57, 58, 60, 62, 65-67, 69-71, 74, 76, 79, 80, 84, 86, 89-92, 95, 97, 98, 101, 110, 111, 113-119, 121-128, 130-134, 136, 138, 139, 141, 143, 146-151, 153, 154, 157-160, 162-164, 167-178, 180, 181, 183, 186-190, 192, 193, 195-220, 224, 226-231, 234, 236, 237, 240, 241, 244-246, 248, 254, 255, 261, 262, 266, 270, 275, 280, 282, 283, 288, 289, 290, 292, 295, 301, 303, 304, 309, 311, 341-782, 784, 785, 790, 792, 794, 796, 800-804, 807, 808 and 810-826;
- (ii) sequences that hybridize to a sequence recited in any one of SEQ ID NOs: 1, 11-13, 15, 20, 23-27, 29, 30, 33, 34, 39, 41, 43-46, 51, 52, 57, 58, 60, 62, 65-67, 69-71, 74, 76, 79, 80, 84, 86, 89-92, 95, 97, 98, 101, 110, 111, 113-119, 121-128, 130-134, 136, 138, 139, 141, 143, 146-151, 153, 154, 157-160, 162-164, 167-178, 180, 181, 183, 186-190, 192, 193, 195-220, 224, 226-231, 234, 236, 237, 240, 241, 244-246, 248, 254, 255, 261, 262, 266, 270, 275, 280, 282, 283, 288, 289, 290, 292, 295, 301, 303, 304, 309, 311, 341-782, 784, 785, 790, 792, 794, 796, 800-804, 807, 808 and 810-826 under moderately stringent conditions; and
 - (iii) complements of sequences of (i) or (ii);
 - (b) polynucleotides encoding a polypeptide of (a); and
 - (c) antigen presenting cells that express a polypeptide of (a);

under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells.

- 36. An isolated T cell population, comprising T cells prepared according to the method of claim 35.
- 37. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a T cell population according to claim 36.

38. A method for inhibiting the development of a cancer in a patient, comprising the steps of:

- (a) incubating CD4⁺ and/or CD8+ T cells isolated from a patient with at least one component selected from the group consisting of:
- (i) polypeptides comprising at least an immunogenic portion of a lung tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:
- (1) sequences recited in SEQ ID NOs: 1, 11-13, 15, 20, 23-27, 29, 30, 33, 34, 39, 41, 43-46, 51, 52, 57, 58, 60, 62, 65-67, 69-71, 74, 76, 79, 80, 84, 86, 89-92, 95, 97, 98, 101, 110, 111, 113-119, 121-128, 130-134, 136, 138, 139, 141, 143, 146-151, 153, 154, 157-160, 162-164, 167-178, 180, 181, 183, 186-190, 192, 193, 195-220, 224, 226-231, 234, 236, 237, 240, 241, 244-246, 248, 254, 255, 261, 262, 266, 270, 275, 280, 282, 283, 288, 289, 290, 292, 295, 301, 303, 304, 309, 311, 341-782, 784, 785, 790, 792, 794, 796, 800-804, 807, 808 and 810-826;
- (2) sequences that hybridize to a sequence recited in any one of SEQ ID NOs: 1, 11-13, 15, 20, 23-27, 29, 30, 33, 34, 39, 41, 43-46, 51, 52, 57, 58, 60, 62, 65-67, 69-71, 74, 76, 79, 80, 84, 86, 89-92, 95, 97, 98, 101, 110, 111, 113-119, 121-128, 130-134, 136, 138, 139, 141, 143, 146-151, 153, 154, 157-160, 162-164, 167-178, 180, 181, 183, 186-190, 192, 193, 195-220, 224, 226-231, 234, 236, 237, 240, 241, 244-246, 248, 254, 255, 261, 262, 266, 270, 275, 280, 282, 283, 288, 289, 290, 292, 295, 301, 303, 304, 309, 311, 341-782, 784, 785, 790, 792, 794, 796, 800-804, 807, 808 and 810-826 under moderately stringent conditions; and
 - (3) complements of sequences of (1) or (2);
 - (ii) polynucleotides encoding a polypeptide of (i); and
 - (iii) antigen presenting cells that expresses a polypeptide of (i); such that T cells proliferate; and
- (b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of a cancer in the patient.

39. A method for inhibiting the development of a cancer in a patient, comprising the steps of:

- (a) incubating CD4⁺ and/or CD8+ T cells isolated from a patient with at least one component selected from the group consisting of:
- (i) polypeptides comprising at least an immunogenic portion of a lung tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:
- (1) sequences recited in SEQ ID NOs: 1, 11-13, 15, 20, 23-27, 29, 30, 33, 34, 39, 41, 43-46, 51, 52, 57, 58, 60, 62, 65-67, 69-71, 74, 76, 79, 80, 84, 86, 89-92, 95, 97, 98, 101, 110, 111, 113-119, 121-128, 130-134, 136, 138, 139, 141, 143, 146-151, 153, 154, 157-160, 162-164, 167-178, 180, 181, 183, 186-190, 192, 193, 195-220, 224, 226-231, 234, 236, 237, 240, 241, 244-246, 248, 254, 255, 261, 262, 266, 270, 275, 280, 282, 283, 288, 289, 290, 292, 295, 301, 303, 304, 309, 311, 341-782, 784, 785, 790, 792, 794, 796, 800-804, 807, 808 and 810-826;
- (2) sequences that hybridize to a sequence recited in any one of SEQ ID NOs: 1, 11-13, 15, 20, 23-27, 29, 30, 33, 34, 39, 41, 43-46, 51, 52, 57, 58, 60, 62, 65-67, 69-71, 74, 76, 79, 80, 84, 86, 89-92, 95, 97, 98, 101, 110, 111, 113-119, 121-128, 130-134, 136, 138, 139, 141, 143, 146-151, 153, 154, 157-160, 162-164, 167-178, 180, 181, 183, 186-190, 192, 193, 195-220, 224, 226-231, 234, 236, 237, 240, 241, 244-246, 248, 254, 255, 261, 262, 266, 270, 275, 280, 282, 283, 288, 289, 290, 292, 295, 301, 303, 304, 309, 311, 341-782, 784, 785, 790, 792, 794, 796, 800-804, 807, 808 and 810-826 under moderately stringent conditions; and
 - (3) complements of sequences of (1) or (2);
 - (ii) polynucleotides encoding a polypeptide of (i); and
 - (iii) antigen presenting cells that express a polypeptide of (i); such that T cells proliferate;
 - (b) cloning at least one proliferated cell to provide cloned T cells; and
- (c) administering to the patient an effective amount of the cloned T cells, and thereby inhibiting the development of a cancer in the patient.

40. A method for determining the presence or absence of a cancer in a patient, comprising the steps of:

- (a) contacting a biological sample obtained from a patient with a binding agent that binds to a lung tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs: 1, 11-13, 15, 20, 23-27, 29, 30, 33, 34, 39, 41, 43-46, 51, 52, 57, 58, 60, 62, 65-67, 69-71, 74, 76, 79, 80, 84, 86, 89-92, 95, 97, 98, 101, 110, 111, 113-119, 121-128, 130-134, 136, 138, 139, 141, 143, 146-151, 153, 154, 157-160, 162-164, 167-178, 180, 181, 183, 186-190, 192, 193, 195-220, 224, 226-231, 234, 236, 237, 240, 241, 244-246, 248, 254, 255, 261, 262, 266, 270, 275, 280, 282, 283, 288, 289, 290, 292, 295, 301, 303, 304, 309, 311, 341-782, 784, 785, 790, 792, 794, 796, 800-804, 807, 808 and 810-826 or a complement of any of the foregoing polynucleotide sequences;
- (b) detecting in the sample an amount of polypeptide that binds to the binding agent; and
- (c) comparing the amount of polypeptide to a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient.
 - 41. A method according to claim 40, wherein the binding agent is an antibody.
- 42. A method according to claim 43, wherein the antibody is a monoclonal antibody.
 - 43. A method according to claim 40, wherein the cancer is lung cancer.
- 44. A method for monitoring the progression of a cancer in a patient, comprising the steps of:
- (a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to a lung tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any

one of SEQ ID NOs: 1, 11-13, 15, 20, 23-27, 29, 30, 33, 34, 39, 41, 43-46, 51, 52, 57, 58, 60, 62, 65-67, 69-71, 74, 76, 79, 80, 84, 86, 89-92, 95, 97, 98, 101, 110, 111, 113-119, 121-128, 130-134, 136, 138, 139, 141, 143, 146-151, 153, 154, 157-160, 162-164, 167-178, 180, 181, 183, 186-190, 192, 193, 195-220, 224, 226-231, 234, 236, 237, 240, 241, 244-246, 248, 254, 255, 261, 262, 266, 270, 275, 280, 282, 283, 288, 289, 290, 292, 295, 301, 303, 304, 309, 311, 341-782, 784, 785, 790, 792, 794, 796, 800-804, 807, 808 and 810-826 or a complement of any of the foregoing polynucleotide sequences;

- (b) detecting in the sample an amount of polypeptide that binds to the binding agent;
- (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and
- (d) comparing the amount of polypeptide detected in step (c) to the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.
 - 45. A method according to claim 44, wherein the binding agent is an antibody.
- 46. A method according to claim 45, wherein the antibody is a monoclonal antibody.
 - 47. A method according to claim 44, wherein the cancer is a lung cancer.
- 48. A method for determining the presence or absence of a cancer in a patient, comprising the steps of:
- (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a lung tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 1, 11-13, 15, 20, 23-27, 29, 30, 33, 34, 39, 41, 43-46, 51, 52, 57, 58, 60, 62, 65-67, 69-71, 74, 76, 79, 80, 84, 86, 89-92, 95, 97, 98, 101, 110, 111, 113-119, 121-128, 130-134, 136, 138, 139, 141, 143, 146-151, 153, 154, 157-160, 162-164, 167-

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- (b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; and
- (c) comparing the amount of polynucleotide that hybridizes to the oligonucleotide to a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient.
- 49. A method according to claim 48, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a polymerase chain reaction.
- 50. A method according to claim 48, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a hybridization assay.
- 51. A method for monitoring the progression of a cancer in a patient, comprising the steps of:
- (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a lung tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 1, 11-13, 15, 20, 23-27, 29, 30, 33, 34, 39, 41, 43-46, 51, 52, 57, 58, 60, 62, 65-67, 69-71, 74, 76, 79, 80, 84, 86, 89-92, 95, 97, 98, 101, 110, 111, 113-119, 121-128, 130-134, 136, 138, 139, 141, 143, 146-151, 153, 154, 157-160, 162-164, 167-178, 180, 181, 183, 186-190, 192, 193, 195-220, 224, 226-231, 234, 236, 237, 240, 241, 244-246, 248, 254, 255, 261, 262, 266, 270, 275, 280, 282, 283, 288, 289, 290, 292, 295, 301, 303, 304, 309, 311, 341-782, 784, 785, 790, 792, 794, 796, 800-804, 807, 808 and 810-826 or a complement of any of the foregoing polynucleotide sequences;

(b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide;

- (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and
- (d) comparing the amount of polynucleotide detected in step (c) to the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.
- 52. A method according to claim 51, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a polymerase chain reaction.
- 53. A method according to claim 51, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a hybridization assay.
 - 54. A diagnostic kit, comprising:
 - (a) one or more antibodies according to claim 11; and
 - (b) a detection reagent comprising a reporter group.
- 55. A kit according to claim 54, wherein the antibodies are immobilized on a solid support.
- 56. A kit according to claim 54, wherein the detection reagent comprises an anti-immunoglobulin, protein G, protein A or lectin.
- 57. A kit according to claim 54, wherein the reporter group is selected from the group consisting of radioisotopes, fluorescent groups, luminescent groups, enzymes, biotin and dye particles.
- 58. An oligonucleotide comprising 10 to 40 contiguous nucleotides that hybridize under moderately stringent conditions to a polynucleotide that encodes a lung tumor

protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs: 1, 11-13, 15, 20, 23-27, 29, 30, 33, 34, 39, 41, 43-46, 51, 52, 57, 58, 60, 62, 65-67, 69-71, 74, 76, 79, 80, 84, 86, 89-92, 95, 97, 98, 101, 110, 111, 113-119, 121-128, 130-134, 136, 138, 139, 141, 143, 146-151, 153, 154, 157-160, 162-164, 167-178, 180, 181, 183, 186-190, 192, 193, 195-220, 224, 226-231, 234, 236, 237, 240, 241, 244-246, 248, 254, 255, 261, 262, 266, 270, 275, 280, 282, 283, 288, 289, 290, 292, 295, 301, 303, 304, 309, 311, 341-782, 784, 785, 790, 792, 794, 796, 800, 802, 804, 807, 808 and 811-826, or a complement of any of the foregoing polynucleotides.

- 59. A oligonucleotide according to claim 58, wherein the oligonucleotide comprises 10-40 contiguous nucleotides recited in any one of SEQ ID NO: 1, 11-13, 15, 20, 23-27, 29, 30, 33, 34, 39, 41, 43-46, 51, 52, 57, 58, 60, 62, 65-67, 69-71, 74, 76, 79, 80, 84, 86, 89-92, 95, 97, 98, 101, 110, 111, 113-119, 121-128, 130-134, 136, 138, 139, 141, 143, 146-151, 153, 154, 157-160, 162-164, 167-178, 180, 181, 183, 186-190, 192, 193, 195-220, 224, 226-231, 234, 236, 237, 240, 241, 244-246, 248, 254, 255, 261, 262, 266, 270, 275, 280, 282, 283, 288, 289, 290, 292, 295, 301, 303, 304, 309, 311, 341-782, 784, 785, 790, 792, 794, 796, 800, 802, 804, 807, 808 and 811-82.
 - 60. A diagnostic kit, comprising:
 - (a) an oligonucleotide according to claim 59; and
- (b) a diagnostic reagent for use in a polymerase chain reaction or hybridization assay.

SEQUENCE LISTING

<110> Corixa Corporation Wang, Tongtong Bangur, Chaitanya S. Lodes, Michael A. Fanger, Gary Vedvick, Tom Carter, Darrick Retter, Marc Mannion, Jane <120> COMPOSITIONS AND METHODS FOR THERAPY AND DIAGNOSIS OF LUNG CANCER <130> 210121.478PC <140> PCT <141> 2000-06-29 <160> 827 <170> FastSEQ for Windows Version 3.0 <210> 1 <211> 527 <212> DNA <213> Homo sapien <400> 1 ccaccagtcc acaaatgtga ctggtaaggg atctagtaac agaggatgga gttggqcaqa 60 atattatect ggatgatatg cacceageae tagaatacae ettteattag aatgaagaga 120 acagacaaag ccctcagaaa agatacaaag gcagagacat tgattagaac attatctcat 180 aacagaggtg gggccattac ccaccattat tgtaaaataa ctgtaactaa ccaaaacaca 240 tacaggette tttaatggag ttaataaaac tatqqcacat tqqqaatcag qqqcaqaqqt 300 actgttccca gacggaaaac tgggataaag ggagccatgc tgacagggcc ttattccagt 360 ctaggttgtt agaaaggagc cctagcccag aaatgacagc aaatagccat aatcattatg 420 tggggctgaa ccagaggaag ccaggctgag ccaagaagct ggaagtatct tgaacggctc 480 tccaaatcca aagattatcc atactcttta tccctccagc gatgtgt 527 <210> 2 <211> 490 <212> DNA <213> Homo sapien ccaagagttc tccactgtga agactgaaaq qacctggtga catttcqgca tcaqtcctqt 60 taccacttgg aggtaacaga agcaggetcg tgtcctcctt taattctacc acactacatq 120 actogoaatt ggttotgaaa ttagaacgtt caccatogta ottaaaatot taggggoatg 180 aagagtcagc tagaacaagg aaaaagaaag tcgcaggtag taggtaagta ggtgggcaca 240 tgaaaagcca agctgctctg tccaacacca gtgtacatgt gctttaacta aatgaactcc 300 agaggccaac agcagcagac ctgctcaatt caccttccaa atcagaacaa gaccaaaaag 360 ctcaggcttg agttgtcaac tatgcatagg ttccgccagt gctgaggggt gtgaggctct 420 agttgtgaag aagctacaag aaatcatgat gcatgtgatc tgggccgcac tggcatttgc 480 agctattcag 490

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19

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      <223> n = A, T, C \text{ or } G
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                                                                        60
ctttggagaa ggacatgtga tgtgatggtc ttcacgttcc acatgtactc gggcaaatag
                                                                       120
ggggacaaac tgaagttaaa caggtcgaaa ctagaggagc tgctgaccct ggagctgacc
                                                                       180
actttcttgg ggaaaaggac acatgaaggt gctttgcaaa agctgatgag caatctggac
                                                                       240
accaacatag gacaacaacg t
                                                                       261
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<213> Homo sapien

<212> DNA <213> Homo sapien <400> 115 cottotoctgt gggttccaga coctgttcca gcaacaattg ctgggacacc tqqqccqact 60 gctccacctc gccaggccct ggccctctcc atctcagccc tgacagccac ccagtgataa 120 acacagcagg cttcctaagc aatgtgacgc accagagggg tggtggtaca cgttcccctt 180 gaagtcatct gaaaattaga gaacagattt gcctcatagc tgaagagaga ccctattcca 240 agcatgaatg gccttgacaa tgttcct 267 <210> 116 <211> 239 <212> DNA <213> Homo sapien <400> 116 ctgatgacct ggggtctagt gaaaatgcag ggtcagattc aqtqqqtctq qqqtctqaat 60 ctctaaggcg ctgccaagtg atgctgatgc tcctggcttg tggaccaccc tgtgtatagc 120 aaagctctag actaggaggt ctcaaccttg gctgcacaga attatctggg gagtttttaa 180 atttcccagt gcccaggctg cattcatatc atagtagaga cagggttttg ccatgctgg 239 <210> 117 <211> 168 <212> DNA <213> Homo sapien <400> 117 aaaaaacttt tatattgctg catcttccac agttctttqg qtaqtctctq aacttaaaat 60 . . ttgtaggagt tgtagactac ctaaattttt aagttatgga tttgttcata ggttgtaggg 120 gtaggtaaag aaggaaacag acaagaaaat ggcttcttqa qgtqqcaq 168 <210> 118 <211> 150 <212> DNA · <213> Homo sapien <400> 118 aaaaaaaaga gtttatttag aaagtatcat agtgtaaaca aacaaattgt accactttga 60 ttttcttgga atacaagact cgtgatgcaa agctgaagtg tqtgtacaag actcttqaca 120 gttgtgcttc tctaggaggt tgggtttttt 150 <210> 119 <211> 154 <212> DNA <213> Homo sapien <400> 119 aaactgtgtg agatattaac cagccgccct gttataaaat caggaaatcc aaacagcgat 60 ttacaccgat taacaccccc ttttatattt tttcaaatac actgagaaaa taatcaaacg 120 ttttcatctc tcttgtcttt ttttgttttt tcct 154 <210> 120 <211> 314 <212> DNA

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tccaaaataa ttttcacccc tctaagcatg taaattcaaa gatggatcct tcatagaaat
                                                                       120
taaaaaaatca atttgagctc atttcgaata cagaacaagt atggcacaga tggaagtcct
                                                                       180
gccacgtttc ctttaatgat gctgactctt gtatcacaca ggccagcatg aagtttctta
                                                                       240
ctcagacttt acaggcattt tccgtaattc aatcagtcct gctcccagca caacacagga
                                                                       300
                                                                       314
ggtgattcga gaat ·
      <210> 121
      <211> 601
      <212> DNA
      <213> Homo sapien
      <400> 121
                                                                        60
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attcaaatct tacaccattt gccccttcta tgaatttatg tataaaattt tttaagagtc
                                                                       120
agagtttttt tttcttgatt aattggatgt atttcacaga atttccaact gctcacgtta
                                                                       180
gttttcttcc ttttagagtt gatctctcta atgtattaga tcttcatgcc tttgatagtc
                                                                       240
tctctggaat aagtttgcag aaaaaacttc agcatgtgcc aggaacacaa cctcaccttg
                                                                       300
atcagagtat tgtacaatca catttgacgt accaggaaat gcaaaggaag aacatcttaa
                                                                       360
                                                                       420
tatgtttatt cagaatcttc tgtgggaaaa gaatgtgaga aacaaggaca atcactgcat
ggaggtcata aggctgaagg gattggtgtc aatcaacgac aaatcacaac aagtgattgt
                                                                       480
ccagggtgtc catgagctct gtgatctgga ggagactcca gtgagctgga aggatgacac
                                                                       540
tgagagaaca aatcgattgg tcctcattgg cagaaattta gataaggata tccttaaaca
                                                                       600
                                                                       601
      <210> 122
      <211> 486
      <212> DNA
      <213> Homo sapien
      <400> 122
ctgtttctaa ttgcttttgt gactgttacc ttttagttca tgcccccca aagagctaaa
                                                                        60
tttcacattt ttacctacaa aattgatttt taattcctgc aaataattta ccattatgag
                                                                       120
ctacaaggtg ggcaacagcg cctgaggatc taattttatg catattactc ccaagtattt
                                                                       180
taacacttgt tggagaagca atatctggat caataaaaca ctgtcccatc aaccatttga
                                                                       240
gtggggagag ggagaagctc ttctgtaagt aagattctgg caagctcttt gaaatgagtc
                                                                       300
ttctttccca cagattttct ctactctttc aatacaaaca gataggagaa gagggaatag
                                                                       360
                                                                       420
aaacctggag gaacttgaat atttttgttc tagatagaga tacagttatt gaaaaggaaa
cctagaaagt agtcacacgt cgcttattta ggccagaagt aattgtactg ggcaaaaatt
                                                                       480
                                                                       486
tcactt
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      <211> 239
      <212> DNA
      <213> Homo sapien
      <400> 123
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aagttgccca cagtatctcc acttaaacta ggctagtaac caaaataatg tggaccttct
                                                                       120
ttaggaaaca gtgtgggaga ataggagtcc agccgtaaga taaactggaa atatttgggc
                                                                       180
gtcttgtacc tggctacgca ccacctcagt gttgttccta cataaacaag gcccctttt
                                                                       239
```

```
<211> 610
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(-610)
      <223> n = A, T, C \text{ or } G
      <400> 124
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                                                                      60
ggaaatcgcc acngngcttt cggttttctt ggtgaaggaa tacaccgcgc cgacaqcaqq
                                                                     120
ttttcagtca gggtcaggga ctgttgcttg cgcgcgaaaa tcaccggtac gccgaggttc
                                                                     180
aggccggtca tgatcgccgg tgcaatgccc gaggcttcga tggtgacgat cttggtgatg
                                                                     240
cccgaatcct tgaacaacgc agcgaattca tcaccgatca gtttcatcag cgccgggtcg
                                                                     300
atctggtggt tcagaaaggc gtcgaccttg agtacctgat cggaaagcac gatgccttct
                                                                     360
tcgcgaattt tcttgtgcag tgcttccacg aaagcttcct ctgttggcgc aacacgcgcc
                                                                     420
gaaagtagat taaaaagtag tcgattctag cgctttaaca tcgcgcgtat atccgccagg
                                                                     480
gcggtattgc cgcgaacggc tttgacttcg gttggtgtt cgtcgttgcc ttcccatgcc
                                                                     540
aggtcatccg gcggcagttc gtcaaggaac cggctggggg cacaatcaat gatctcgccg
                                                                     600
tactgcttgc
                                                                     610
      <210> 125
      <211> 196
      <212> DNA
      <213> Homo sapien
      <400> 125
ctatagggct cgagcggccg cccgggcagg taaaaaatca gcccctaatt tctccatgtt
                                                                      60
tacacttcaa tetgcagget tettaaagtg acagtateet taacetgeca ceagtgteca
                                                                     120
ccctccggcc cccgtcttgt aaaaagggga ggagaattag ccaaacactg taagctttta
                                                                     180
agaagaacaa agtttt
                                                                     196
      <210> 126
      <211> 247
      <212> DNA
      <213> Homo sapien
      <400> 126
aaattagtta aaaaaatgca ttcctcattt gatatagcca cattccaaat gcttaaaagc
                                                                      60
cgcatgtatc tagtgactac catactggag agtacaaata tagaacttta cccqtcactq
                                                                     120
cagacagttc tgttggattg tgcagcattg gacaatatat acagtttgcc tgtatatgag
                                                                     180
240
aggcatc
                                                                     247
     <210> 127
     <211> 590
     <212> DNA
     <213> Homo sapien
     <400> 127
cctccacggc atggcgcaat tgttgttcag gggccgccag gttgctgccc atgccgatgt
                                                                     60
agatacgttc cacgtgetta etegecagae geactegaag egtegecage getaegtttg
                                                                    120
cgcttgctgc cactgctgcg gcgacgcttt ttcgggccat cgccggtggc ttcgcctttg
                                                                    180
etgetgaget etttgateat etegeggege tggetgtegt tggegteetg gtagteggte
                                                                    240
```

```
300
caccactege caaggeegte ggtetgtteg ceggegettt caegeageag caggaagtea
tagcccggca cggaagcgcg ggttgtccag caacaggtcg gcacgtttgc cgctgcggcg
                                                                        360
tggcaggcgc tcctgcatgt cccagatttc acggatcggc atggtgaagc gtttcgggat
                                                                        420
ggcgatgcgc tggcattgct cggcgatcag ctcgtgagca gcttcctgca tggctggaat
                                                                        480
tgccggcatg ccacggtctt gcaggcgcat gacgcgtttc gaaagcgcgg gccacaacag
                                                                        540
ggcggcaaag aggaacgccg gggtgaccgg tttgttctgc ttgatgcgca
                                                                        590
      <210> 128
      <211> 361
      <212> DNA
      <213> Homo sapien
      <400> 128
                                                                        60
ctgcccatgg aaaccctcca ggagctgctg gacctgcaca ggaccagtga gagggaggcc
                                                                       120
attgaagtct tcatgaaaaa ctctttcaag gatgtaacca aagtttccag aaagaattgg
agactctact agatgcaaaa cagaatgaca tttgtaaacg gaacctggaa gcatcctcgg
                                                                       180
attattgctc ggctttactt aaggatattt ttggtcccct agaagaagca gtgaagcagg
                                                                       240
gaatttattc taagccagga ggccataatc tcttcattca gaaaacagaa gaactgaagg
                                                                       300
caaagtacta tcgggagcct cggaaaggaa tacaggctga agaagttctg cagaaatatt
                                                                       360
                                                                       361
t
      <210> 129
      <211> 546
      <212> DNA
      <213> Homo sapien
      <400> 129
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                                                                        60
caaaaaagta tccagtgttt cttttcttat gaagatataa taaaacacag tattggtaag
                                                                       120
                                                                       180 .
cacattttaa cagtatgctt ttcttttgta gggaaaggag atatggctat gtctaacatc
gtgggatcca atgtgtttga tatgttgtgc cttggtattc catggtttat taaaactgca
                                                                       240
                                                                       300
tttataaatg gatcagctcc tgcagaagta aacagcagag gactaactta cataaccatc
tototoaaca titoaattat tittotitti titagoagtio acticaatgg ciggaaacta ...
                                                                       360
                                                                       420
gacagaaagt tgggaatagt ctgcctatta tcatacttgg ggcttgctac attatcagtt
ctatatgaac ttggaattat tggaaataat aaaataaggg gctgtggagg ttgatattat
                                                                       480
                                                                       540
taatagtgtt atgcagaaaa tatgaatggc agggagggc agagagaaaa atccatttct
                                                                       546
tcattt
      <210> 130
      <211> 733
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(733)
      <223> n = A, T, C \text{ or } G
      <400> 130
                                                                        60
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                                                                       120
actttcaaag acaccacatc ctaatgccat cacatcagaa tttaggcttc aacatatgaa
                                                                       180
ttttgggggg acacaaacat tcacctcata gcattcattg tttcttgtta ttggcaaagc
caagactcac attgtctaag ttatttgact tttgagtccg cagatgtgaa aacagtgcta
                                                                       240
                                                                       300
aacagtccag cttcatgagt ggagaacagc atttgtgaca accaccaaag tacctctgtg
                                                                       360
gtcagtgtcc tcaaccaggg cacagcatca tggaccagag cctctgcagg gcacagagga
```

```
gtggtgagga acaggggctc tggagcaacc ccacttccct ctgctttgta tatggggggt
                                                                      420
tctgcacatg actgcatttg aaaagggctt cactgcgctt gctgaaggag tgcacttgag
                                                                      480
ctagcggaga gttcccagag ggtgtctgga agaagcaaag gctattcttt gtttcactca
                                                                      540
gttatagatg gaagtcagac acttctgcct gaagtacttt cacacactcc acagtcttaa
                                                                      600
gaaggatgga naaagcatgc caactactca naaaaccaca ggtgttcaag caatggtatc
                                                                      660
cttttatncc tacaactagt ggacaaagng gggcctctgt aatttgggaa agctaggaaa
                                                                     720
actttttctg ggg
                                                                      733
      <210> 131
      <211> 305
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(305)
      \langle 223 \rangle n = A,T,C or G
      <400> 131
aaacacatac gaatanttna actgtgatta tgaagtgaca gccggctaaa tatgtcttgt
                                                                      60
attitctctc ticctittt tgctaactca tcctttattc cattcctgct tccatggtaa
                                                                     120
tgcaggctca aataaattac taggatacaa gattacttca agcctctttt ctgtggaact
                                                                     180
cataatatga taagcatttg ttacaagatt gcctgtagtt gtttagggga caaattatat
                                                                     240
tagggaaaga aagtetttet ttagttggtt aaatttteta ttataattgg gtactaaatt
                                                                     300
tattt
                                                                     305
      <210> 132
      <211> 545
      <212> DNA
      <213> Homo sapien
      <400> 132
aaacaatgct acactcattt ttggcaaagt gctgtattgt tcagtctgtg tacaaaactg
                                                                      60
accatctatg aaccaatcag tataaaaaat ttctataaaa acaaaattta gacagcggct
                                                                     120
caagaaaaca agctgccatt tatgcataga ttgatgtaca gtaacctaac caaatgtccc
                                                                     180
ttttgaattt tcaagttact gaaaaaaaat gtgtcgagaa acacattaag aaggcacatg
                                                                     240
tacagtctac aatactcttc agtctcccta actcatgccc tgcccctata aaggaaatat
                                                                     300
360
caattattaa agttcaaaat ctctggagga aaatacaagc aaaaccactc atacactcca
                                                                     420
agectgaaac acacatctaa ceteeccagg taetggtttg gtttteagag gteeacctag
                                                                     480
aaaacaaatc taaaacttca ggcaaaacag agcaaaactg gacatttaac aattacacaa
                                                                     540
ttttt
                                                                     545
     <210> 133
     <211> 330
     <212> DNA
     <213> Homo sapien
     <220>
     <221> misc_feature
     <222> (1)...(330)
     <223> n = A, T, C \text{ or } G
      <400> 133
                                                                      60
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tgtaacanat agttcaggaa accctactat aaggtttatc aaatggtctc ataaacagtt
acttattcaa gcacgccaaa gctcagtgaa aagtattttt cacccttact ctttctcgtg
                                                                        180
                                                                        240
tcattcaaag agaagttttg atgtagtgta tttatttgta gggagtaatg aacagatcca
tttcacagta gactttgtgc tctaggtgat gcagctaatt gccccagttt ggaaaacatg
                                                                        300
                                                                        330
gacttggatg aattgtcttt tgtttgggac
      <210> 134
      <211> 627
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(627)
      <223> n = A,T,C or G
      <400> 134
                                                                         60
aaatattact tcaaatacat tttaaagctc aacaaacttg tgttgaactg aattgcagat
                                                                        120
cctgaactct atttgaaaat acatcatgaa acagaaaanc ccattccaaa tgaaaatgat
                                                                        180
agtgctttgt tgggggtggg aatgaggcgg ggagactaaa tcactattaa cagacttctt
ttcccaatgc aatttgtcaa aagttcaaaa gttctgaaat gtactaaatc ttaagcaaat
                                                                        240
                                                                        300
taaattcatg atattactaa aactttttaa atagtgcaat gacttatcaa gttatagtgg
ctgcattaag aacaaattat tgtgtgaaat acctgtataa acacaaaata caattaaata
                                                                        360
tttctttaca aaaagctgag cattacgcat aatagtggaa tgtctttcat taggtgtatt
                                                                        420
                                                                        480
ttttaaagat taacaaaagt aacatttcct aaaatgtata catgtgccat atttttgcaa
acatgcctga gaatgtattt aaaacatttc tgtagtaaga gtttgcaaga acttcacaaa
                                                                        540
cctgcaaata aaatgcatct ttttaaaaaag gtgaaaatgg catctccaca ctgcaacaat
                                                                        600
                                                                        627
tcaaaaagtg cagcatccct aatcttt
      <210> 135
      <211> 277
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(277)
      <223> n = A, T, C \text{ or } G
      <400> 135
aaaatcaaat atattattig ttaaaaatca gcttgtttca ttacnggaaa ttacaccagt
                                                                         60
                                                                        120
ccqttctatt tactttcaaa ccatattcaa ctcctcaact ttcaaacatg taatcaacta
                                                                        180
atttcaaaag ggaaaaggta ccctttataa aggagagatc tgttaagaca ccaagaaatc
                                                                        240
aaaattaata tcacttaata attaagtgga taacacatgc ctcccaatac agtgcagtga
                                                                        277
gaaacacaaa acatcaattc ccgcgtactc tgcgttg
      <210> 136
      <211> 486
      <212> DNA
      <213> Homo sapien
      <400> 136
                                                                         60
aaaacagaat gaattcattg ttacagttac agaagtcaga agcccaaata cagtctgcct
gaaccaaagc cagggtcagc aaggttcctt tccactgttt tgccaacttc tagaggccac
                                                                        120
ctgtattcct tggttcatgg cccctctctt catcatcaaa taatcagcat agctttatga
                                                                        180
```

```
cattggcage tetgattttg etettttgee tteetettat gtagaeeett gtaattaeat
                                                                        240
tgggtacacc cagataaccc caaataatct ccctatctca agattcttaa tgtaattata
                                                                        300
ttgggaaagt cccttttgtc atataagata acatagcaat ggattccaag gattagtatg
                                                                        360
tgagtttctt ttgaggggct ataattaacc ctaccacaat atggaaatgt ctattgtttt
                                                                        420
tctatgtacc agaaataaga cattaggatg tgaaattaat aacataacac cacttacggc
                                                                        480
atcacc
                                                                        486
      <210> 137
      <211> 552
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(552)
      <223> n = A, T, C \text{ or } G
      <400> 137
ccatcttgca tcaaatgttc ttaaggcagt gactggctat caaccacagt ttctgtctcc
                                                                         60
ccagttgcaa acacaggatc catgcaacag ttctgagacc atacacttag aaaccacagg
                                                                        120
ggatgcggat caaatgcaga actcccaaat tataaaacag tcaggctaca ctcaaaacaa
                                                                        180
aacatagaac atcaacaaca cacatctccc aaaaaagaag tgcaacgcat gcttgtataa
                                                                        240 .
accaacaata acaaaaaaac cacaataaaa aatgcagagt ctcccaaaca agttttcaaa
                                                                        300
tgtattgcan aaagaaaaaa aatgtatata tatataaaat taaaaagtct gaaatactag
                                                                        360
tgcatagtca attacctaac accaagtttc ttttctttct gtccaagctc tactgcccct
                                                                        420
ctgatactag cagcatgtct acaggctaag accatagcag caaaaaacgt ttttcatttg
                                                                        480
gcatttacaa aattaaatta ctgaataaaa atataatttt ttataaaact atttcttaca
                                                                        540
gtaataattt tt
                                                                       552
      <210> 138
      <211> 231
      <212> DNA
      <213> Homo sapien
      <400> 138
aaattttact agtgttactt aatgtatatt ctaaaaagag aatgcagtaa ctaatgccct
                                                                        60
aaatgtttga tctctgtttg tcattacttt ttcaaaatat ttttttctgt aaagtataat
                                                                       120
atataaaact tcttgcttaa attgaatttc tatattagtg gttaattgca gtttattaaa
                                                                       180
gggatcatta tcagtaattt catagcaact gttctagtgt tttgtgtttt t
                                                                       231
      <210> 139
      <211> 535
      <212> DNA
      <213> Homo sapien
      <400> 139
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                                                                        60
tggtgatccg gcaaggggtg aaaccaaaga gcgggggctg tgaggccctt cgcaqtccct
                                                                       120
cgtaagtcgc tgcgatggag tgaactatca cgcatcgtgt ttatttcgtc aacacgaaat
                                                                       180
gtgatttatt tttgcgaatt aacacggcag ttctcggtta cgttttcgga aagcgtggga
                                                                       240
tatgattctg tctatcctgt acggatatac agtaattacc gggaggggat tccatggcga
                                                                       300
agaagcaggc ggcaccggca gcacggcagg aaatgagcgg tatggcgcgc ctcgggcttc
                                                                       360
gcgtctcatc gatgattaat cacccggtcg cccagacgca gcgctgggtt acgattcatc
                                                                       420
gcctggacac ggatggggat cgggagtggg aagaggttct gagcgtgatc gctgataccq
                                                                       480
acgagetega getgaegete aatgaegatg geagtgtgae ggtgaggtgg gagea
                                                                       535
```

<220>

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<210> 140
      <211> 640
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(640)
      <223> n = A, T, C \text{ or } G
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                                                                          60
catgacgtag aaaaggatga aaaacttatt cgtctaatgg aagagatcat gagtgagaag
                                                                         120
gagaataaaa ccattgtttt tgtggaaacc aaaagaagat gtgatgagct taccagaaaa
                                                                         180
atgaggagag atgggtggcc tgccatgggt atccatggtg acaagagtca acaagagcgt
                                                                         240
gactgggttc taaatgaatt caaacatgga aaagctccta ttctgattgc tacagatgtg
                                                                         300
gcctccagag ggctaggtta gtacaaactc gcattcatgg cttggtttcc cagaagatct
                                                                         360
ccatttaact tttttaaaga aagtttattg ctttctttaa cctgcatttt ttctaagttt
                                                                         420
tttttcgcat aaaggtgctg tctttgtggc aaggcctagg catgacaatc ggaggactcg
                                                                         480
agggggatgg aggactagtg atccggctgg ctgcttccag tcgattagag aggtgaaaaa
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51

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52

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                                                                       180
ggcgagatcc aagctggagc tgcagctctg agtcccataa attctttgtg cttctgtaaa.
                                                                       240
gaataaatct gtttttaatg caaattaaaa ctactggcag ggaattttgg ctcccagtta
                                                                       300
ttaaaagact ggaaatgtgt aagtggagaa aggcaataac tgcagtaatc tcttaccgga
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ctctattata attccaaaca tacataatgg tgagaaaaac cgggaaggga agaatgtggc
                                                                       420
aatgtccact ctttgcccca aacataaccc ttaatttcca tggcgggccc aaacactggt
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aaaaaccaaa atggtaccct ctatagcatg caacttttat ttcactccaa acgaaaaatt
                                                                       540
attttgacta tggcttggga aatccattag tagaagaagt tttataacct ataggaaccc
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ggccatttca tttctaccaa atcacaggaa ttttagaatg ggcaaggaat ttacaggaag
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gaatctgaag attgctttgg gtagtatgaa cattttaaca atattgattc ttccgattaa
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                                                                       360
tategetatt getaaatgga atgaettttt aaatttettt tteacattge teetgqtqqe
                                                                       420
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ccttcaaaca cggataattt gacttcttcc ccatccaatt gggaggccct ttatatcttc
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687

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tcaacgccaa caagaccaat tcagatcctg atctgactgg tttctaatac aatctctttc
                                                                     360
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                                                                     420
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229
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ataaagactg tgtttgcaaa	tacttagcct	gcacttcaag	ataccaggca	tctaagcacg	420
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caagtaagtg atggaacagt					600
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taaatatgtg caactccttg					780
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gatttttagc cttcttgcca					300
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cagtccaagg agctgtacgg cacctgggag atgctgtg	tg ggaacgaggt gcagatcctg 540
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gtactgaggt tcattgccag ggcaggaggt atttccagaa aatactcatg cctgtgttct
                                                                        180.
                                                                        225
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      <211> 678
      <212> DNA
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ctgtatcatt tcttccagaa cacttcctaa ctcatcgtat gaggccagca tcactctaat
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                                                                       240
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                                                                       300
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                                                                       360
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                                                                       420
agatacagtg aaggaggaag aaataaaatt ttctttgcgc ataacatgat tcttctatgt
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ggaaatcaca gagatttgaa catttttttt ttttgagaca gtttttgctc ttgttgccca
                                                                       540
ggttggagtg taatggcgcg atctcggctc actgcaacct tcacctcccg aattcaaggt
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                                                                       660
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678
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caatcctttt gttttagtga gttgattttc aatagaaaaa tacaaatgaa catgtgttta
                                                                       300
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tttgccctct acgtgggcta cacccgcgtg tctgattaca aacaccactg gagcgatgtc
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ttcttcaaag cccgaccccc acagcactgt ctgaaggagg aggagctgga acggaagccc
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agectgteac tgaegttgae cetgggegag getgaecaea accaetatgg ataccegeae
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gtttctcagg caatcctgta ttttaatttt agatgtattt cctgaagcat attttcata
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gaaattaaaa aggacttgga tgccaagaag aaacccccta gtgcatgaga ctgcctccag
                                                                       180
cactgccttc aggatatact gattctactg ctcttgaggg cctcgtttac tatctgaacc
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tttgcttt
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gttaaaaata gacaacaact gctagatata ttcaaaattc tattttttt tctgagcata
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<213> Homo sapien

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caatatgtca gataaaacca gtgaagatat atgtctacaa ctcagtcgtt tactagaaag
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tgaaagaaac attttactca gagaggcaaa catttctgat ctaggagtaa qtttcccact
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cactttgcaa ggacccactc attctgcana aagacctaca agtctttctg qtctcaattq
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caaagtacgt gaaaatgtgt atgaaagatc taaaagctaa atattagaat aaggctaatt
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atttttattt cagatgtatt t
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      <211> 543
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cttattcaat attttgagcc aatgggggag ttatgtagat ttttttccct acacattagc
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tggccccttt tatgaccaat gactcataag gcaagatgtg tggtggcatc ttcggacagg
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cagcaggett taatagggca gcctgggttg gtggaggcaa gcaaagctaa ttggcatgcg
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tgggaatcaa accccaggcc ctgggctcat tagcccatgg tcaaaacaac tgagccagag
                                                                       360
gaggtaataa tttgcccaag aatatcagta gttcctttat tagaagaaaa tqqctqatat
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ggaagttggg gaatctgaat tgccagagaa tcttgggaag agtaataagc tcttagtctc
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acaggcaata tcagaggctc					. 240
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cagtgtgtgg ggcagatggc at	tcacctacc	tgtctgcctg	ctttgctggc	tgcaacagca	240
cgaatctcac gggctgtgcg to	gcctcacca (ccgtccctgc	tgagaacgca	accgtggttc	300
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<213> Homo sapien

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gcaggaaagt ttaagtggat gtaagttttt ataaggaaag taataagagg aggctgcttt
                                                                         180
tgaaggtcct ttgatcttcc atgatgataa tatcgttgca aagttcttta acttgtattc
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agcctcagaa atggcctttc tgtggtgaag aaagaggtct cggaggaagt tgcggagctc
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agcag
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      <211> 75
      <212> DNA
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tgatctcagc actgaacgat ttcaagccct acgcaccana acagaaggag ggtggaggaa
                                                                        180
gtgatcanag ggaacgagct gtaggtttgc anaaatgtgt gaaaccaaaa tgatcactgc
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      <211> 535
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<400> 307

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tttcagagag agactttatt gcaactgtga ccaccgtcac tggtgagcac tgctgttcgg
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cccccagcgg acttaaaaga ctggaatgtg gtagtggcgg tcgttctcgg tcagcaggga
                                                                       240
                                                                       300
gateteegge cagteeetga gaggeteete tgggtageag aetteaaagt etetggagtt
aaacttgaac aqtctgaaca cttttatctt tacttcaagg gagtatccaa gtataaacat
                                                                       360
atcaatctgc tctagtccac atgtgtcgcc tacagaattc aggtgattca tcatgaagct
                                                                       420
caaaggatca gaggatgtct ccctggaaaa caggagtcta aaaagactgg gaatgacctt
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                                                                       240
atatgtgact aaatcatttg gaatatgccc agaccccaag aatatttatg cccaacttga
                                                                       300
atgctaacca gaagtccctt actgtagaag attgtaaggt tgctattttt ttgccccgac
                                                                       360
accaaaatat tgatgtattt tccaacacca attctccaat tctctgacac caactcgatg
                                                                       420
                                                                       480
ttcaacaatt cagttatatt ctgtcactaa ttcctgcagc tatcagcagg ccccacaggt
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      <212> DNA
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                                                                       165
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      <212> DNA
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                                                                       120
acccacacga cagagacgtc actcaagcag cacagccaca aatagtttac agcagctcat
                                                                       180
gcccggcatc cgcccatgct gggagactcc ctgaaaggtg ggcacctgcc gtctatgagg
                                                                       240
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      <210> 307
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cacatttata totgacacco gaccatactt toagtcacca qaatatotto totocaqatt
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t
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      <211> 390
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                                                                       120
gaaccgtggt atgtctgcat gttgcccctt tctcttttcc cctttcctgt cccaccatac
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gagcacctcc agcctgaaca gaagctctta ctctttccta tttcagtgtt acctgtgtgc
                                                                       240
ttggtctgtt tgactttacg cccatctcag gacacttccg tagactgttt aggttcccct
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gtcaaatatc agttacccac teggteecag ttttgttgee eeagaaaggg atqttattat
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      <210> 311
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Asn Pro Leu Val Leu Pro Glu Tyr Leu Ile His Ala Phe Phe Cys Val

Met Phe Leu Cys Ala Ala Glu Trp Leu Thr Leu Gly Leu Asn Met Pro 70 75

Leu Leu Ala Tyr His Ile Trp Arg Tyr Met Ser Arg Pro Val Met Ser

Gly Pro Gly Leu Tyr Asp Pro Thr Thr Ile Met Asn Ala Asp Ile Leu 105

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Lys Met Tyr Asn His Ser Trp Pro Glu Ser Leu Ala Cys Asp Glu Leu 115 120 125

Pro Val Tyr Asp Arg Gly Val Cys Ile Ser Pro Glu Ala Ile Val Thr

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Val Gln Glu Arg Pro Leu Asp Val Asp Cys Lys Arg Leu Ser Pro Asp 165 170 175

Arg Cys Lys Cys Lys Lys Val Lys Pro Thr Leu Ala Thr Tyr Leu Ser 180 185 190

Lys Asn Tyr Ser Tyr Val Ile His Ala Lys Ile Lys Ala Val Gln Arg 195 200 205

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Gln	Cys 210	Gly	Tyr	Lys	Lys	Pro 215	Pro	Met	Thr	Cys	Leu 220	Val	Leu	Ile	Cys
Glu 225	Pro	Ile	Pro	His	Pro 230	Ser	Asn	Ile	Glu	Ile 235	Pro	Leu	Asp	Ser	Lys 240
Thr	Phe	Leu	Ser	Arg 245	His	Ser	Leu	Asp	Met 250	Lys	Phe	Ser	Tyr	Cys 255	Asp
Glu _.	Arg	Ile	Thr 260	Glu	Leu	Met	Gly	Tyr 265	Glu	Pro	Glu	Glu	Leu 270	Leu	Gly
Arg	Ser	Ile 275	Tyr	Glu	Tyr	Tyr	His 280	Ala	Leu	Asp	Ser	Asp 285	His	Leu	Thr
Lys	Thr 290	His	His	Asp	Met	Phe 295	Thr	Lys	Gly	Gln	Val 300	Thr	Thr	Gly	Gln
Tyr 305	Arg	Met	Leu	Ala	Lys 310	Arg	Gly	Gly	Tyr	Val 315	Trp	Val	Glu	Thr	Gln 320
Ala	Thr	Val	Ile	Tyr 325	Asn	Thr	Lys	Asn	Ser		Pro	Gln	Cys	Ile	Val

Cys	Val	Asn	Tyr 340	Val	Val	Ser	Gly	Ile 345	Ile	Gln	His	Asp	Leu 350	Ile	Phe
Ser	Leu	Gln 355	Gln	Thr	Glu	Cys	Val 360	Leu	Lys	Pro	Val	Glu 365	Ser	Ser	Asp
Met	Lys 370	Met	Thr	Gln	Leu	Phe 375	Thr	Lys	Val	Glu	Ser 380	Glu	Asp	Thr	Ser
Ser 385	Leu	Phe	Asp	Lys	Leu 390	Lys	Lys	Glu	Pro	Asp 395	Ala	Leu	Thr	Leu	Leu 400
Ala	Pro	Ala	Ala	Gly 405	Asp	Thr	Ile	Ile	Ser 410	Leu	Asp	Phe	Gly	Ser 415	Asn
Asp	Thr	Glu	Thr 420	Asp	Asp	Gln	Gln	Leu 425	Glu	Glu	Val	Pro	Leu 430	Tyr	Asn
Asp	Val	Met 435	Leu	Pro	Ser	Pro	Asn 440	Glu	Lys	Leu	Gln	Asn 445	Ile	Asn	Leu
Ala	Met 450	Ser	Pro	Leu	Pro	Thr 455	Ala	Glu	Thr	Pro	Lys 460	Pro	Leu	Arg	Ser
Ser 465	Ala	Asp	Pro	Ala	Leu 470	Asn	Gln	Glu	Val	Ala 475	Leu	Lys	Leu	Glu	Pro 480
Asn	Pro	Glu	Ser	Leu 485	Glu	Leu	Ser	Phe	Thr 490	Met	Pro	Gln	Ile	Gln 495	Asp
Gln	Thr	Pro	Ser 500	Pro	Ser	Asp	Gly	Ser 505	Thr	Arg	Gln	Ser	Ser 510	Pro	Glu
Pro	Asn	Ser 515	Pro	Ser	Glu	Tyr	Cys 520	Phe	Tyr	Val	Asp	Ser 525	Asp	Met	Val
Asn	Glu 530	Phe	Lys	Leu	Glu	Leu 535	Val	Glu	Lys	Leu	Phe 540	Ala	Glu	Asp	Thr
Glu 545	Ala	Lys	Asn	Pro	Phe 550	Ser	Thr	Gln	Asp	Thr 555		Leu	Asp	Leu	Glu 560
Met	Leu	Ala	Pro	Tyr 565	Ile	Pro	Met	Asp	Asp 570	Asp	Phe	Gln	Leu	Arg 575	Ser
Phe	Asp	Gln	Leu 580	Ser	Pro	Leu	Glu	Ser 585	Ser	Ser	Ala	Ser	Pro 590	Glu	Ser
Ala	Ser	Pro 595	Gln	Ser	Thr	Val	Thr 600	Val	Phe	Gln	Gln	Thr 605	Gln	Ile	Gln
Glu	Pro 610	Thr	Ala	Asn	Ala	Thr 615	Thr	Thr	Thr	Ala	Thr 620	Thr	Asp	Glu	Leu

Lys Thr Val Thr Lys Asp Arg Met Glu Asp Ile Lys Ile Leu Ile Ala

630 635 Ser Pro Ser Pro Thr His Ile His Lys Glu Thr Thr Ser Ala Thr Ser 645 650 Ser Pro Tyr Arg Asp Thr Gln Ser Arg Thr Ala Ser Pro Asn Arg Ala 660 · 665 670 Gly Lys Gly Val Ile Glu Gln Thr Glu Lys Ser His Pro Arg Ser Pro 680 Asn Val Leu Ser Val Ala Leu Ser Gln Arg Thr Thr Val Pro Glu Glu 695 Glu Leu Asn Pro Lys Ile Leu Ala Leu Gln Asn Ala Gln Arg Lys Arg 705 710 715 Lys Met Glu His Asp Gly Ser Leu Phe Gln Ala Val Gly Ile Gly Thr 725 730 Leu Leu Gln Gln Pro Asp Asp His Ala Ala Thr Thr Ser Leu Ser Trp 740 745 Lys Arg Val Lys Gly Cys Lys Ser Ser Glu Gln Asn Gly Met Glu Gln 760 Lys Thr Ile Ile Leu Ile Pro Ser Asp Leu Ala Cys Arg Leu Leu Gly 770 775 Gln Ser Met Asp Glu Ser Gly Leu Pro Gln Leu Thr Ser Tyr Asp Cys 790 795 Glu Val Asn Ala Pro Ile Gln Gly Ser Arg Asn Leu Leu Gln Gly Glu Glu Leu Leu Arg Ala Leu Asp Gln Val Asn 820 825 <210> 331 <211> 92 <212> PRT <213> Homo sapiens Met Ala Tyr Arg Gly Gln Gly Gln Lys Val Gln Lys Val Met Val Gln 5 Pro Ile Asn Leu Ile Phe Arg Tyr Leu Gln Asn Arg Ser Arg Ile Gln

Val Trp Leu Tyr Glu Gln Val Asn Met Arg Ile Glu Gly Cys Ile Ile 35 40 45

106

Gly Phe Asp Glu Tyr Met Asn Leu Val Leu Asp Asp Ala Glu Glu Ile 50 55 60

His Ser Lys Thr Lys Ser Arg Lys Gln Leu Gly Arg Ile Met Leu Lys 65 70 75 80

Gly Asp Asn Ile Thr Leu Leu Gln Ser Val Ser Asn 85 90

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<213> Homo sapiens

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Thr Glu Ala Ala Leu Gly Asp Ala Ala Gln Glu Pro Thr Gly Asn Asn 20 25 30

Ala Glu Ile Cys Leu Leu Pro Leu Asp Tyr Gly Pro Cys Arg Ala Leu
35 40 45

Leu Leu Arg Tyr Tyr Tyr Asp Arg Tyr Thr Gln Ser Cys Arg Gln Phe 50 55 60

Leu Tyr Gly Gly Cys Glu Gly Asn Ala Asn Asn Phe Tyr Thr Trp Glu 65 70 75 80

Ala Cys Asp Asp Ala Cys Trp Arg Ile Glu Lys Val Pro Lys Val Cys 85 90 95

Arg Leu Gln Val Ser Val Asp Asp Gln Cys Glu Gly Ser Thr Glu Lys
100 105 110

Tyr Phe Phe Asn Leu Ser Ser Met Thr Cys Glu Lys Phe Phe Ser Gly 115 120 125

Gly Cys His Arg Asn Arg Ile Glu Asn Arg Phe Pro Asp Glu Ala Thr 130 135 140

Cys Met Gly Phe Cys Ala Pro Lys Lys Ile Pro Ser Phe Cys Tyr Ser 145 150 155 160

Pro Lys Asp Glu Gly Leu Cys Ser Ala Asn Val Thr Arg Tyr Tyr Phe 165 170 175

Asn Pro Arg Tyr Arg Thr Cys Asp Ala Phe Thr Tyr Thr Gly Cys Gly
180 185 190

Gly Asn Asp Asn Asn Phe Val Ser Arg Glu Asp Cys Lys Arg Ala Cys 195 200 205

Ala Lys Ala Leu Lys Lys Lys Lys Met Pro Lys Leu Arg Phe Ala

	Ser 225	Arg	Ile	Arg	Lys	Ile 230		Lys	Lys	Gln	Phe 235					
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		0> 3 Gln		Ala	Ara	Pro	Thr	Leu	Tro	Ala	Δla	Δla	T.e.u	Thr	T.eu	Leu
			3		5					10		712.0	БСС	****	15	Бец
7	/al	Leu	Leu	Arg 20	Gly	Pro	Pro	Val	Ala 25		Ala	Gly	Ala	Ser 30		Gly
C	Sly	Leu	Gly 35		Val	Val	Arg	Cys 40	Glu	Pro	Cys	Asp	Ala 45	Arg	Ala	Leu
I	Ala	Gln 50	Cys	Ala	Pro	Pro	Pro 55	Ala	Val	Cys	Ala	Glu 60	Leu	Val	Arg	Glu
F	°ro 65	Gly	Cys	Gly	Cys	Cys 70	Leu	Thr	Cys	Ala	Leu 75	Ser	Glu	Gly	Gln	Pro 80
C	ys	Gly	Ile	Tyr	Thr 85	Glu	Arg	Cys	Gly	Ser 90	Gly	Leu	Arg	Cys	Gln 95	Pro
S	er	Pro	Asp	Glu 100	Ala	Arg	Pro	Leu	Gln 105	Ala	Leu	Leu	Asp	Gly 110	Arg	Gly
L	eu	Cys	Val 115	Asn	Ala	Ser	Ala	Val 120	Ser	Arg	Leu	Arg	Ala 125	Tyr	Leu	Leu
P	ro	Ala 130	Pro	Pro	Ala	Pro	Gly 135	Asn	Ala	Ser	Glu	Ser 140	Glu	Glu	Asp	Arg
	er 45	Ala	Gly	Ser	Val	Glu 150	Ser	Pro	Ser	Val	Ser 155	Ser	Thr	His	Arg	Val 160
S	er	Asp	Pro	Lys	Phe 165	His	Pro	Leu	His	Ser 170	Lys	Ile	Ile	Ile	Ile 175	Lys
L	ys	Gly	His	Ala 180	Lys	Asp	Ser	Gln	Arg 185	Tyr	Lys	Val [*]	Asp	Tyr 190	Glu	Ser
G	ln	Ser	Thr 195	Asp	Thr	Gln	Asn	Phe 200	Ser	Ser	Glu	Ser	Lys 205	Arg	Glu	Thr
G	lu	Tyr 210	Gly	Pro	Cys	Arg	Arg 215	Glu	Met	Glu	Asp	Thr 220	Leu	Asn	His	Leu
L	vs	Phe	Leu	Asn	Val	Leu	Ser	Pro	Ara	Glv	Val	Hie	Tle	Pro	λan	Cve

225 230 235 240 Asp Lys Lys Gly Phe Tyr Lys Lys Gln Cys Arg Pro Ser Lys Gly 250 245 Arg Lys Arg Gly Phe Cys Trp Cys Val Asp Lys Tyr Gly Gln Pro Leu 265 260 Pro Gly Tyr Thr Thr Lys Gly Lys Glu Asp Val His Cys Tyr Ser Met 280 Gln Ser Lys 290 <210> 334 <211> 582 <212> PRT <213> Homo sapiens <400> 334 Glu Ser Lys Gly Ala Ser Ser Cys Arg Leu Leu Phe Cys Leu Leu Ile 10 Ser Ala Thr Val Phe Arg Pro Gly Leu Gly Trp Tyr Thr Val Asn Ser 25 Ala Tyr Gly Asp Thr Ile Ile Ile Pro Cys Arg Leu Asp Val Pro Gln 35 40 45 Asn Leu Met Phe Gly Lys Trp Lys Tyr Glu Lys Pro Asp Gly Ser Pro 50 55 Val Phe Ile Ala Phe Arg Ser Ser Thr Lys Lys Ser Val Gln Tyr Asp Asp Val Pro Glu Tyr Lys Asp Arg Leu Asn Leu Ser Glu Asn Tyr Thr 90 Leu Ser Ile Ser Asn Ala Arg Ile Ser Asp Glu Lys Arg Phe Val Cys 100 105 110 Met Leu Val Thr Glu Asp Asn Val Phe Glu Ala Pro Thr Ile Val Lys 115 120 Val Phe Lys Gln Pro Ser Lys Pro Glu Ile Val Ser Lys Ala Leu Phe 135 Leu Glu Thr Glu Gln Leu Lys Lys Leu Gly Asp Cys Ile Ser Glu Asp 145 150 155 160 Ser Tyr Pro Asp Gly Asn Ile Thr Trp Tyr Arg Asn Gly Lys Val Leu 170 175 165 His Pro Leu Glu Gly Ala Val Ile Ile Phe Lys Lys Glu Met Asp

			180					185	•				190)	
Pro	Val	Thr 195		Leu	Tyr	Thr	Met 200		Ser	Thr	Leu	Glu 205		· Lys	Thr
Thr	Lys 210		Asp	Ile	Gln	Met 215		Phe	Thr	. Cys	Ser 220		Thr	Туг	Tyr
Gly 225		Ser	Gly	Gln	Lys 230	Thr	Ile	His	Ser	Glu 235		Ala	Val	Phe	Asp 240
Ile	Tyr	Tyr	Pro	Thr 245	Glu	Gln	Val	Thr	Ile 250		Val	Leu	Pro	Pro 255	Lys
Asn	Ala	Ile	Lys 260	Glu	Gly	Asp	Asn	Ile 265		Leu	Lys	Cys	Leu 270	_	Asn
Gly	Asn	Pro 275	Pro	Pro	Glu	Glu	Phe 280	Leu	Phe	Tyr	Leu	Pro 285	_	Gln	Pro
Glu	Gly 290	Ile	Arg	Ser	Ser	Asn 295	Thr	Tyr	Thr	Leu	Thr 300	Asp	Val	Arg	Arg
Asn 305	Ala	Thr	Gly	Asp	Tyr 310	Lys	Cys	Ser	Leu	Ile 315	Asp	Lys	Lys	Ser	Met 32.0
Ile	Ala	Ser	Thr	Ala 325	Ile	Thr	Val	His	Tyr 330	Leu	Asp	Leu	Ser	Leu 335	Asn
Pro	Ser	Gly	Glu 340	Val	Thr	Arg	Gln	Ile 345		Asp	Ala	Leu	Pro 350	Val	Ser
Cys	Thr	Ile 355	Ser	Ala	Ser	Arg	Asn 360	Ala	Thr	Val	Val	Trp 365	Met	Lys	Asp
Asn	Ile 370	Arg	Leu	Arg	Ser	Ser 375	Pro	Ser	Phe	Ser	Ser 380	Leu	His	Tyr	Gln
Asp 385	Ala	Gly	Asn	Tyr	Val 390	Cys	Glu	Thr	Ala	Leu 395	Gln	Glu	Val	Glu	Gly 400
Leu	Lys	Lys	Arg	Glu 405	Ser	Leu	Thr	Leu	Ile 410	Val	Glu	Gly	Lys	Pro 415	Gln
Ile	Lys	Met	Thr 420	Lys	Lys	Thr	Asp	Pro 425	Ser	Gly	Leu	Ser	Lys 430	Thr	Ile
Ile	Cys	His 435	Val	Glu	Gly	Phe	Pro 440	Lys	Pro	Ala	Ile	Gln 445	Trp	Thr	Ile
	Gly 450	Ser	Gly	Ser	Val	Ile 455	Asn	Gln	Thr	Glu	Glu 460	Ser	Pro	Tyr	Ile
Asn 465	Gly	Arg	Tyr		Ser 470	Lys	Ile	Ile	Ile	Ser 475	Pro	Glu	Glu	Asn	Val 480

Thr Leu Thr Cys Thr Ala Glu Asn Gln Leu Glu Arg Thr Val Asn Ser 485 490 495

Leu Asn Val Ser Ala Ile Ser Ile Pro Glu His Asp Glu Ala Asp Glu
500 505 510

Ile Ser Asp Glu Asn Arg Glu Lys Val Asn Asp Gln Ala Lys Leu Ile 515 520 525

Val Gly Ile Val Val Gly Leu Leu Leu Ala Ala Leu Val Ala Gly Val 530 540

Val Tyr Trp Leu Tyr Met Lys Lys Ser Lys Thr Ala Ser Lys His Val 545 550 555 560

Asn Lys Asp Leu Gly Asn Met Glu Glu Asn Lys Lys Leu Glu Glu Asn 565 570 575

Asn His Lys Thr Glu Ala 580

<210> 335

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<213> Homo sapiens

<400> 335

Met Ala Glu Val Glu Asp Gln Ala Ala Arg Asp Met Lys Arg Leu Glu 5 10 15

Glu Lys Asp Lys Glu Arg Lys Asn Val Lys Gly Ile Arg Asp Asp Ile
20 .25 30

Glu Glu Glu Asp Asp Gln Glu Ala Tyr Phe Arg Tyr Met Ala Glu Asn
35 40 45

Pro Thr Ala Gly Val Val Glu Glu Glu Glu Asp Asn Leu Glu Tyr 50 55 60

Asp Ser Asp Gly Asn Pro Ile Ala Pro Thr Lys Lys Ile Ile Asp Pro 65 70 75 80

Leu Pro Pro Ile Asp His Ser Glu Ile Asp Tyr Pro Pro Phe Glu Lys 85 90 95

Asn Phe Tyr Asn Glu His Glu Glu Ile Thr Asn Leu Thr Pro Gln Gln
100 105 110

Leu Ile Asp Leu Arg His Lys Leu Asn Leu Arg Val Ser Gly Ala Ala 115 120 125

Pro Pro Arg Pro Gly Ser Ser Phe Ala His Phe Gly Phe Asp Glu Gln 130 135 140

145	Met	uis	GIII	116	150	пуз	261	Giu	lyl	155	GIII	PIO	1111	FIO	160
Gln	Cys	Gln	Gly	Val 165	Pro	Val	Ala	Leu	Ser 170	Gly	Arg	Asp	Met	Ile 175	Gly
Ile	Ala	Lys	Thr 180	Gly	Ser	Gly	Lys	Thr 185	Ala	Ala	Phe	Ile	Trp 190	Pro	Met
Leu	Ile	His 195	Ile	Met	Asp	Gln	Lys 200	Glu	Leu	Glu	Pro	Gly 205	Asp	Gly	Pro
Ile	Ala 210	Val	Ile	Val	Cys	Pro 215	Thr	Arg	Glu	Leu	Cys 220	Gln	Gln	Ile	His
Ala 225	Glu	Cys	Lys	Arg	Phe 230	Gly	Lys	Ala	Tyr	Asn 235	Leu	Arg	Ser	Val	Ala 240
Val	Tyr	Gly	Gly	Gly 245	Ser	Met	Trp	Glu	Gln 250	Ala	Lys	Ala	Leu	Gln 255	Glu
Gly	Ala	Glu	Ile 260	Val	Val	Cys	Thr	Pro 265	Gly	Arg	Leu	Ile	Asp 270	His	Val
Lys	Lys	Lys 275	Ala	Thr	Asn	Leu	Gln 280	Arg	Val	Ser	Tyr	Leu 285	Val	Phe	Asp
Glu	Ala 290	Asp	Arg	Met	Phe	Asp 295	Met	Gly	Phe	Glu	Tyr 300	Gln	Val	Arg	Ser
Ile 305	Ala	Ser	His	Val	Arg 310	Pro	Asp	Arg	Gln	Thr 315	Leu	Leu	Phe	Ser	Ala 320
Thr	Phe	Arg	Lys	Lys 325	Ile	Glu	Lys	Leu	Ala 330	Arg	Asp	Ile	Leu	Ile 335	Asp
Pro	Ile	Arg	Val 340	Val	Gln	Gly	Asp	Ile 345	Gly	Glu	Ala	Asn	Gļu 350	Asp	Val
Thr	Gln	Ile 355	Val	Glu	Ile	Leu	His 360	Ser	Gly	Pro	Ser	Lys 365	Trp	Asn	Trp
Leu	Thr 370	Arg	Arg	Leu	Val	Glu 375	Phe	Thr	Ser	Ser	Gly 380	Ser	Val	Leu	Leu
Phe 385	Val	Thr	Lys	Lys	Ala 390	Asn	Ala	Glu	Glu	Leu 395	Ala	Asn	Asn	Leu	Lys 400
Gln	Glu	Gly	His	Asn 405	Leu	Gly	Leu	Leu	His 410	Gly	Asp	Met	Asp	Gln 415	Ser
Glu	Arg	Asn	Lys	Val	Ile	Ser	Asp	Phe	Lys	Lys	Lys	Asp	Ile	Pro	Val

480

WO 01/00828 PCT/US00/18061

Leu Val Ala Thr Asp Val Ala Ala Arg Gly Leu Asp Ile Pro Ser Ile 435

Lys Thr Val Ile Asn Tyr Asp Val Ala Arg Asp Ile Asp Thr His Thr 450

His Arg Ile Gly Arg Thr Gly Arg Ala Gly Glu Lys Gly Val Ala Tyr

Thr Leu Leu Thr Pro Lys Asp Ser Asn Phe Ala Gly Asp Leu Val Arg

470

Thr Leu Leu Thr Pro Lys Asp Ser Ash Phe Ala Gly Asp Leu Val Arg
485 490 495

Asn Leu Glu Gly Ala Asn Gln His Val Ser Lys Glu Leu Leu Asp Leu 500 505 510

Ala Met Gln Asn Ala Trp Phe Arg Lys Ser Arg Phe Lys Gly Gly Lys 515 520 525

Gly Lys Lys Leu Asn Ile Gly Gly Gly Gly Leu Gly Tyr Arg Glu Arg 530 540

Pro Gly Leu Gly Ser Glu Asn Met Asp Arg Gly Asn Asn Asn Val Met 545 550 555

Ser Asn Tyr Glu Ala Tyr Lys Pro Ser Thr Gly Ala Met Gly Asp Arg 565 570 575

Leu Thr Ala Met Lys Ala Ala Phe Gln Ser Gln Tyr Lys Ser His Phe 580 585 590

Val Ala Ala Ser Leu Ser Asn Gln Lys Ala Gly Ser Ser Ala Ala Gly
595 600 605

Ala Ser Gly Trp Thr Ser Ala Gly Ser Leu Asn Ser Val Pro Thr Asn 610 615 620

Ser Ala Gln Gln Gly His Asn Ser Pro Asp Ser Pro Val Thr Ser Ala 625 630 635 640

Ala Lys Gly Ile Pro Gly Phe Gly Asn Thr Gly Asn Ile Ser Gly Ala 645 650 655

Pro Val Thr Tyr Pro Ser Ala Gly Ala Gln Gly Val Asn Asn Thr Ala 660 665 670

Ser Gly Asn Asn Ser Arg Glu Gly Thr Gly Gly Ser Asn Gly Lys Arg 675 680 685

Glu Arg Tyr Thr Glu Asn Arg Gly Ser Ser Pro Ser Gln Ser Arg Arg
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Asp Trp Gln Ser Ala 705

<210> 336

<211> 480

<212> PRT

<213> Homo sapiens

<400> 336

Met Ile Arg Ala Ala Pro Pro Pro Leu Phe Leu Leu Leu Leu Leu 5 10 15

Leu Leu Leu Val Ser Trp Ala Ser Arg Gly Glu Ala Ala Pro Asp Gln
20 25 30

Asp Glu Ile Gln Arg Leu Pro Gly Leu Ala Lys Gln Pro Ser Phe Arg
35 40 45

Gln Tyr Ser Gly Tyr Leu Lys Ser Ser Gly Ser Lys His Leu His Tyr 50 55 60

Trp Phe Val Glu Ser Gln Lys Asp Pro Glu Asn Ser Pro Val Val Leu 65 70 75 80

Trp Leu Asn Gly Gly Pro Gly Cys Ser Ser Leu Asp Gly Leu Leu Thr
85 90 95

Glu His Gly Pro Phe Leu Val Gln Pro Asp Gly Val Thr Leu Glu Tyr 100 105 110

Asn Pro Tyr Ser Trp Asn Leu Ile Ala Asn Val Leu Tyr Leu Glu Ser 115 120 125

Pro Ala Gly Val Gly Phe Ser Tyr Ser Asp Asp Lys Phe Tyr Ala Thr 130 135 140

Asn Asp Thr Glu Val Ala Gln Ser Asn Phe Glu Ala Leu Gln Asp Phe 145 150 155 160

Phe Arg Leu Phe Pro Glu Tyr Lys Asn Asn Lys Leu Phe Leu Thr Gly 165 170 175

Glu Ser Tyr Ala Gly Ile Tyr Ile Pro Thr Leu Ala Val Leu Val Met 180 185 190

Gln Asp Pro Ser Met Asn Leu Gln Gly Leu Ala Val Gly Asn Gly Leu 195 . 200 205

Ser Ser Tyr Glu Gln Asn Asp Asn Ser Leu Val Tyr Phe Ala Tyr Tyr 210 215 220

His Gly Leu Leu Gly Asn Arg Leu Trp Ser Ser Leu Gln Thr His Cys 225 230 235 240

Cys Ser Gln Asn Lys Cys Asn Phe Tyr Asp Asn Lys Asp Leu Glu Cys 245 250 255

Val Thr Asn Leu Gln Glu Val Ala Arg Ile Val Gly Asn Ser Gly Leu

Asn Ile Tyr Asn Leu Tyr Ala Pro Cys Ala Gly Gly Val Pro Ser His

Phe Arg Tyr Glu Lys Asp Thr Val Val Val Gln Asp Leu Gly Asn Ile Phe Thr Arg Leu Pro Leu Lys Arg Met Trp His Gln Ala Leu Leu Arg Ser Gly Asp Lys Val Arg Met Asp Pro Pro Cys Thr Asn Thr Thr Ala Ala Ser Thr Tyr Leu Asn Asn Pro Tyr Val Arg Lys Ala Leu Asn Ile Pro Glu Gln Leu Pro Gln Trp Asp Met Cys Asn Phe Leu Val Asn Leu Gln Tyr Arg Arg Leu Tyr Arg Ser Met Asn Ser Gln Tyr Leu Lys Leu Leu Ser Ser Gln Lys Tyr Gln Ile Leu Leu Tyr Asn Gly Asp Val Asp Met Ala Cys Asn Phe Met Gly Asp Glu Trp Phe Val Asp Ser Leu Asn Gln Lys Met Glu Val Gln Arg Arg Pro Trp Leu Val Lys Tyr Gly Asp Ser Gly Glu Gln Ile Ala Gly Phe Val Lys Glu Phe Ser His Ile Ala Phe Leu Thr Ile Lys Gly Ala Gly His Met Val Pro Thr Asp Lys Pro Leu Ala Ala Phe Thr Met Phe Ser Arg Phe Leu Asn Lys Gln Pro Tyr <210> 337 <211> 543 <212> PRT <213> Homo sapiens <400> 337 Met Ala Ala Ala Lys Ala Glu Met Gln Leu Met Ser Pro Leu Gln Ile Ser Asp Pro Phe Gly Ser Phe Pro His Ser Pro Thr Met Asp Asn Tyr Pro Lys Leu Glu Glu Met Met Leu Leu Ser Asn Gly Ala Pro Gln Phe

		35					40					45			
Leu	Gly 50	Ala	Ala	Gly	Ala	Pro 55	Glu	Gly	Ser	Gly	Ser 60	Asn	Ser	Ser	Ser
Ser 65	Ser	Ser	Gly	Gly	Gly 70	Gly	Gly	Gly	Gly	Gly 75	Gly	Ser	Asn	Ser	Ser 80
Ser	Ser	Ser	Ser	Thr 85	Phe	Asn	Pro	Gln	Ala 90	Asp	Thr	Gly	Glu	Gln 95	Pro
Tyr	Glu	His	Leu 100	Thr	Ala	Glu	Ser	Phe 105	Pro	Asp	Ile	Ser	Leu 110	Asn	Asn
Glu	Lys	Val 115	Leu	Val	Glu	Thr	Ser 120	Tyr	Pro	Ser	Gln	Thr 125	Thr	Arg	Leu
Pro	Pro 130	Ile	Thr	Tyr	Thr	Gly 135	Arg	Phe	Ser	Leu	Glu 140	Pro	Ala	Pro	Asn
Ser 145	Gly	Asn	Thr	Leu	Trp 150	Pro	Glu	Pro	Leu	Phe 155	Ser	Leu	Val	Ser	Gly 160
Leu	Val	Ser	Met	Thr 165	Asn	Pro	Pro	Ala	Ser 170	Ser	Ser	Ser	Ala	Pro 175	Ser
Pro	Ala	Ala	Ser 180	Ser	Ala	Ser	Ala	Ser 185	Gln	Ser	Pro	Pro	Leu 190	Ser	Cys
Ala	Val	Pro 195	Ser	Asn	Asp	Ser	Ser 200	Pro	Ile	Tyr	Ser	Ala 205	Ala	Pro	Thr
Phe	Pro 210	Thr	Pro	Asn	Thr	Asp 215	Ile	Phe	Pro	Glu	Pro 220	Gln	Ser	Gln	Ala
Phe 225	Pro	Gly	Ser	Ala	Gly 230	Thr	Ala	Leu	Gln	Tyr 235	Pro	Pro	Pro	Ala	Tyr 240
Pro	Ala	Ala	Lys	Gly 245	Gly	Phe	Gln	Val	Pro 250	Met	Ile	Pro	Asp	Tyr 255	Leu
Phe	Pro	Gln	Gln 260	Gln	Gly	Asp	Leu	Gly 265	Leu	Gly	Thr	Pro	Asp 270	Gln	Lys
Pro	Phe	Gln 275	Gly	Leu	Glu	Ser	Arg 280	Thr	Gln	Gln	Pro	Ser 285	Leu	Thr	Pro
Leu	Ser 290	Thr	Ile	Lys	Ala	Phe 295	Ala	Thr	Gln	Ser	Gly 300	Ser	Gln	Asp	Leu
Lys 305	Ala	Leu	Asn	Thr	Ser 310	Tyr	Gln	Ser	Gln	Leu 315	Ile	Lys	Pro	Ser	Arg 320
Met	Arg	Lys	Tyr	Pro	Asn	Arg	Pro	Ser	Lys 330	Thr	Pro	Pro	His	Glu 335	Arg

Pro Tyr Ala Cys Pro Val Glu Ser Cys Asp Arg Arg Phe Ser Arg Ser Asp Glu Leu Thr Arg His Ile Arg Ile His Thr Gly Gln Lys Pro Phe Gln Cys Arg Ile Cys Met Arg Asn Phe Ser Arg Ser Asp His Leu Thr Thr His Ile Arg Thr His Thr Gly Glu Lys Pro Phe Ala Cys Asp Ile Cys Gly Arg Lys Phe Ala Arg Ser Asp Glu Arg Lys Arg His Thr Lys Ile His Leu Arg Gln Lys Asp Lys Lys Ala Asp Lys Ser Val Val Ala Ser Ser Ala Thr Ser Ser Leu Ser Ser Tyr Pro Ser Pro Val Ala Thr Ser Tyr Pro Ser Pro Val Thr Thr Ser Tyr Pro Ser Pro Ala Thr Thr Ser Tyr Pro Ser Pro Val Pro Thr Ser Phe Ser Ser Pro Gly Ser Ser Thr Tyr Pro Ser Pro Val His Ser Gly Phe Pro Ser Pro Ser Val Ala Thr Thr Tyr Ser Ser Val Pro Pro Ala Phe Pro Ala Gln Val Ser Ser Phe Pro Ser Ser Ala Val Thr Asn Ser Phe Ser Ala Ser Thr Gly Leu Ser Asp Met Thr Ala Thr Phe Ser Pro Arg Thr Ile Glu Ile Cys <210> 338 <211> 148 <212> PRT <213> Homo sapiens

117

Leu Leu Gln Gly Trp Val Met Tyr Val Ser Leu Thr Ser Phe Leu Ile 50 55

Ser Leu Met Phe Leu Leu Ser Tyr Leu Phe Gly Phe Tyr Lys Arg Phe 70 75

Glu Ser Trp Arg Val Leu Asp Ser Leu Tyr His Gly Thr Thr Gly Ile 90

Leu Tyr Met Ser Ala Ala Val Leu Gln Val His Ala Thr Ile Val Ser 105

Glu Lys Leu Leu Asp Pro Arg Ile Tyr Tyr Ile Asn Ser Ala Ala Ser 120 115

Phe Phe Ala Phe Ile Ala Thr Leu Leu Tyr Ile Leu His Ala Phe Ser 130 135 140

Ile Tyr Tyr His 145

<210> 339

<211> 196

<212> PRT

<213> Homo sapiens

<400> 339

Met Pro Gly Met Phe Phe Ser Ala Asn Pro Lys Glu Leu Lys Gly Thr 5

Thr His Ser Leu Leu Asp Asp Lys Met Gln Lys Arg Arg Pro Lys Thr 20 25

Phe Gly Met Asp Met Lys Ala Tyr Leu Arg Ser Met Ile Pro His Leu

Glu Ser Gly Met Lys Ser Ser Lys Ser Lys Asp Val Leu Ser Ala Ala 50 55

Glu Val Met Gln Trp Ser Gln Ser Leu Glu Lys Leu Leu Ala Asn Gln 65 70 75

Thr Gly Gln Asn Val Phe Gly Ser Phe Leu Lys Ser Glu Phe Ser Glu 90

Glu Asn Ile Glu Phe Trp Leu Ala Cys Glu Asp Tyr Lys Lys Thr Glu 100 105

Ser Asp Leu Leu Pro Cys Lys Ala Glu Glu Ile Tyr Lys Ala Phe Val 115 120

His Ser Asp Ala Ala Lys Gln Ile Asn Ile Asp Phe Arg Thr Arg Glu 135 140 130

Ser Thr Ala Lys Lys Ile Lys Ala Pro Thr Pro Thr Cys Phe Asp Glu 145 150 155 160

Ala Gln Lys Val Ile Tyr Thr Leu Met Glu Lys Asp Ser Tyr Pro Arg 165 170 175

Phe Leu Lys Ser Asp Ile Tyr Leu Asn Leu Leu Asn Asp Leu Gln Ala 180 185 190

Asn Ser Leu Lys 195

<210> 340

<211> 316

<212> PRT

<213> Homo sapiens

<400> 340

Met Ala Thr Phe Val Glu Leu Ser Thr Lys Ala Lys Met Pro Ile Val 5 10 15

Gly Leu Gly Thr Trp Lys Ser Pro Leu Gly Lys Val Lys Glu Ala Val 20 25 30

Lys Val Ala Ile Asp Ala Gly Tyr Arg His Ile Asp Cys Ala Tyr Val 35 40 45

Tyr Gln Asn Glu His Glu Val Gly Glu Ala Ile Gln Glu Lys Ile Gln 50 55 60

Glu Lys Ala Val Lys Arg Glu Asp Leu Phe Ile Val Ser Lys Leu Trp 65 70 75 80

Pro Thr Phe Phe Glu Arg Pro Leu Val Arg Lys Ala Phe Glu Lys Thr 85 90 95

Leu Lys Asp Leu Lys Leu Ser Tyr Leu Asp Val Tyr Leu Ile His Trp
100 105 110

Pro Gln Gly Phe Lys Ser Gly Asp Asp Leu Phe Pro Lys Asp Asp Lys
115 120 125

Gly Asn Ala Ile Gly Gly Lys Ala Thr Phe Leu Asp Ala Trp Glu Ala 130 135 140

Met Glu Glu Leu Val Asp Glu Gly Leu Val Lys Ala Leu Gly Val Ser 145 150 155 160

Asn Phe Ser His Phe Gln Ile Glu Lys Leu Leu Asn Lys Pro Gly Leu 165 170 175

Lys Tyr Lys Pro Val Thr Asn Gln Val Glu Cys His Pro Tyr Leu Thr 180 185 190

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Ala Tyr Ser Pro Leu Gly Ser Pro Asp Arg Pro Trp Ala Lys Pro Glu
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Asp Pro Ser Leu Leu Glu Asp Pro Lys Ile Lys Glu Ile Ala Ala Lys
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                                         235
His Lys Lys Thr Ala Ala Gln Val Leu Ile Arg Phe His Ile Gln Arg
                245
                                     250
Asn Val Ile Val Ile Pro Lys Ser Val Thr Pro Ala Arg Ile Val Glu
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                                 265
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Asn Ile Gln Val Phe Asp Phe Lys Leu Ser Asp Glu Glu Met Ala Thr
                             280
                                                 285
Ile Leu Ser Phe Asn Arg Asn Trp Arg Ala Cys Asn Val Leu Gln Ser
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124

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<210> 371 <211> 518 <212> DNA <213> Homo sapien	
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<210> 372	

<211> 335

<212> DNA

128

<213> Homo sapien

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aagccccgg tatcaccaaa tggctggaat cccctttgc tctccggagc tggtctctgg
                                                                       180
ccctgggggc ggggtggagt ttttaatctg ggatcctggg gcttctggct ccctcgccca
                                                                       240
                                                                       300
taaagcggga caaccttctc tctgctgatc ccagctttac atactggaca ctcttgccgt
                                                                       335
tctggccgtg tctccagcca ctgatgaaga catgg
      <210> 373
      <211> 467
      <212> DNA
      <213> Homo sapien
      <400> 373
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gctaagttga cttaggggct gtgcacagga actaaaaggc aggaaagtac taaatattgc
                                                                       120
tgagagcatc caccccagga aggactttac cttccaggag ctccaaactg gcaccacccc
                                                                       180
                                                                       240
cagtgeteac atggetgact ttatecteeg tgttecattt ggeacageaa gtggeagtgt
ctccaccacc tatgatggtg atgcagcccc tagaagtggc tttcaccacc tcatccatga
                                                                       300
gagetttggt teecegggea aaagetteee atteaaatae eeceacagga eeatteeaca
                                                                       360
                                                                       420
caatctgctt agcccgagtg acagcctcag catacttctt gctgctttca ggaccacagt
                                                                       467
ccaagcccat ccagccagca ggtacgccag aagccacagt ggcttgg
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      <211> 284
      <212> DNA
      <213> Homo sapien
      <400> 374
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                                                                       120
                                                                       180
attccaggct cagtattgtg accgcggagc cacaggggac cccacgcaca ttccgttgcc
                                                                       240
ttacccgatg gcttgtgacg cggagagaac cgattaaaac cgtttgagaa actcctccct
                                                                       284
tgtctagccc tgtgttcgct gtggacgctg tagaggcagg ttgg
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      <211> 307
      <212> DNA
      <213> Homo sapien
      <400> 375
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                                                                       120
ttgatgactt ccgagaagca tattattggc tccgtcataa tactccagag gatgcgaagg
tcatgtcctg gtgggattat ggctatcaga ttacagctat ggcaaaccga acaattttag
                                                                       180
                                                                       240
tggacaataa cacatggaat aatacccata tttctcgagt agggcaggca atggcgtcca
                                                                       300
cagaggaaaa agcctatgag atcatgaggg agctcgatgt cagctatgtg ctggtcattt
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ttggagg
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<212> DNA

<213> Homo sapien

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                                                                         120
atgtactcgg catcgtcatc atagggcttc tgtgccccaa tgcccaccca gaagaagttc
                                                                         180
traggetect caccttegtt gataacetge ttgctgtagg aggtgtcaaa catggtgtte
                                                                         240
aggatgtett etgecaactt ggettegtea gggtetgatg eeeggeecae eeaggeatae
                                                                         300
acgatgccct ggttgtcctc actctcaaag ggaaccttga ggatgaagca gaactcggag
                                                                         360
ttgaggaggc tggagtcggt gttgatctgg atgcaccggg tgcagagggc gctgccgttg
                                                                         420
gtgcggatct ggtagaggct gggctgttgg gcgccctgga ccgccttcct cttgccccgg
                                                                         480
tggatgatga acttcctctt gaaatgggac aggaacttgg ggttctcctg ctgctgcgtc
                                                                         540
atgcgtacca cctccagctt cccagggaag aggctctcga acttcttttg caggctgaag
                                                                         600
gtgaaggtga cccacccata ttgggaggct ttcacggccc tgccagaagt
                                                                         650
       <210> 377
       <211> 306
       <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(306)
      <223> n = A, T, C or G
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gcggccgccc gggcaggttc gggtgctgcc ttcacctgcc aggcccttcc ccgctagctt
                                                                        120
ggggcgagca gagctgcgtc cagtggaact aaagccgttc caggattatc aaaaactgag
                                                                        180
cagcaacctt gggggacctg gatcatcacg gactccccca actggaaggt ccttctctgg
                                                                        240
cctcaattcc cgtctcaagg ccacgccttc cacctacagt ggagtcttcc gcacccagcg
                                                                        300
cgtcga
                                                                        306
      <210> 378
      <211> 199
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(199)
      <223> n = A, T, C \text{ or } G
      <400> 378
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atctccaaat cttgccattt gtatactttt ggtggagact tggatgtcat atcttctttg
                                                                        120
ttttgggttt tcttccctag cttattttgt ggcttttaaa gaagtggatt gtattgtgag
                                                                        180
atcctgtgat tcctggtgg
                                                                        199
      <210> 379
      <211> 216
      <212> DNA
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<213> Homo sapien
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      <221> misc feature
      <222> (1)...(216)
      <223> n = A, T, C \text{ or } G
      <400> 379
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                                                                        120
                                                                        180
cttgccatag cccttttcaa acaactgcac catggtgcgg ccaccatgct tctctggagg
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gtgtagggca ctcaaacgcc gggtgtgtgt acgcag
      <210> 380
      <211> 555
      <212> DNA
      <213> Homo sapien
      <400> 380
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gtgaaaatgg tgatgatatc tttagaaggt gaagatgggt tggatgaaat ttattcattc
                                                                        120
                                                                        180
agtgagagtc tgagaaaact gtgcgtcttc aagaaaattg agaggcattc cattcactgg
ccctqccqac tgaccattqq ctccaatttg tctataagga ttgcagccta taaatcgatt
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ctacaggaga gayttaaaaa gacttggaca gttgtggatg caaaaaccct aaaaaaagaa
                                                                        300
                                                                        360
gatatacaaa aagaaacagt ttattgctta aatgatgatg atgaaactga agttttaaaa
qaqqatatta ttcaagggtt ccgctatgga agtgatatag ttcctttctc taaagtggat
                                                                        420
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qaqqaacaaa tgaaatataa atcggagggg aagtgcttct ctgttttggg attttgtaaa
tcttctcagg gtcagagaag attcttcatg ggaaatcaag ttctaaaggc tttgccccaa
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ccctttctcc acgtggtcct ctatctccgg ctgggccctt tcttacagtt tcctcttgta
                                                                        240
                                                                        300
aagattggca tgttgctagg cataaggtta ctgcaagcag caacaaagtc cgcgtatcca
caaaqctqaq catgtctagc acttagacat gcagactcct tgtgtcgcag agcccctggg
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                                                                        406
tcaccggcgg aggtatcacc tggcgggcgc gggcatgcag tcgtgg
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      <211> 528
      <212> DNA
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      <223> n = A,T,C or G
      <400> 382
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 acattttttc ccccaggggt ggggcaagga cagtggagag agtgctagga aatgagtccc
                                                                        120
 ctgggaaagg ggaccgggcc gtgatgttaa atatctccgg ctcccaagtg actggatttg
                                                                        180
cctaggacct tcagaccaac agacttcaga ccctcagacc tgccccgggg ccaggtggag
                                                                        240
aaagtgaggg ccgtacaagg aagtgaaatt ctgagttgtt ggggctaagc ctgacccct
                                                                        300
ctccatgctc cccgccccaa cccactctgg cctcagtaga ttttttttc agttgtggtt
                                                                        360
gttgcccagg ctggagtgca gtagcgccat cttggctcac tgcacctcca ccttccgggc
                                                                        420
tcaagcgatt ctccagcctc agcctcctga gtagctagga ctgcaggtgc tccaccacgc
                                                                        480
ccggctaatt tttgtatttt tagtagagat ggggtttccc catgttgg
                                                                        528
       <210> 383
      <211> 335
       <212> DNA
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      <221> misc feature
      <222> (1)...(335)
      <223> n = A,T,C or G
      <400> 383
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cagatggaag ctgagctgaa cacattacga tggatgatgg aaacataaga ctatcaagaa
                                                                       120 .
atccaagtgg taatgggcga agtttattca gcatccggca atggacttat cgtagttggg
                                                                       180
gaaacgggtg ttccgaataa tatcctggaa gttatcagga cacctatttt aaatataggc
                                                                       240
ctgaattttg taaagtaata tttaaggtgg tccgtgataa ttaaataaaa tgcttaattc
                                                                       300
atgtggcgaa aaaaaaaaa naaaaaaaaa aaaaa
                                                                       335
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cctccagctc cccaggggca gccccagtag ctacactgtc cagacagcac aagaccaggc
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tggtgtcacg tccatccgag cgctgcctca gggatcgata aagtttcact gcagaaagtc
                                                                       180
tccactgcgg tatgctgaca tctgccctga accttcaccc tacagcatta caggctttaa
                                                                       240
tcagattctg ctggaaagac acaggctgat ccacgtgacc tcttctgcct tcactgggct
                                                                       300
ggggtgatcc ttggtgcctt tgtttccaca agg
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      <211> 343
      <212> DNA
      <213> Homo sapien
      <400> 385
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                                                                       60
aacagccagc cgatatggac ttctagctgc accgggtcac tgagggtgga gaggtttgtc
                                                                       120
tggcacctgt actctccact gtcgtcgact gtggcagcgt caatgaagta gctcgaggcc
                                                                      180
tggcttgaga tgaggctctc attgtgaaac cactgtgtgg aattgtcctc aggggagtag
                                                                      240
gctccctggc acttcagagt cacactgtcc ttctcgagca ccctgtacca ttgaggctcc
                                                                      300
aggaacacca cagcctttgg gagatcttca gtccgcatgc caa
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132

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caagectgac accgtagget etgetetgaa tgacteteet gtgggtetgg etgeetatat
                                                                        240
tctagagaag ttttccacct ggaccaatac ggaattccga tacctggagg atggagg
                                                                        297
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      <212> DNA
      <213> Homo sapien
      <400> 390
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gctggcttcc tggaggcgtt cgcctctagt ttctcaggga tggagcgaga gcccagccag
                                                                       180
agaacagtaa gaggagetge teteetatet geacteacce agg
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      <211> 365
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                                                                       120
ctggggctgc ccagcctgac cgtaggggat ccactggcag agccaaggtg gatgctggtg
                                                                       180 ·
cctgaagctg gaagccagca ggacatgaga cccctcctgt agcaggaagt ggttctagaa
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ctcccagcag aacagaacgg aaaaggagct gattggggat agaatgagtt ctgctaaaca
                                                                       300
gccagatgct ctgagagagg tgacactgga ctgtctcgga ggtgtgtgca gatggctaca
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ggtgg
                                                                       365
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                                                                       120
gatagttttg ctagccaccc taattatcca tattcagatg aatattaaca tggagagctt
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tgcctgatgt ctaccagaag ccctgtgtgt ggatggtgac gcagaggacg tctctatgcc
                                                                       240
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ag
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tctggaagta gtcgatgacc agggggaagt agtcgtcaag cacttggttg cactggggca tgagcagctt caaggggagg acgttgcact cctgctccag gaacttcctc atcgtgtcct ggaaaatggc ctccttgg	240 300 318
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tttaggatgg ggaactcgat gatttcctga ggatgaatct gtggcttgtc gcacgtggcc	240
tcaaagtcca gcactaaaaa gtagtgatac ctctggagag ggaaggacac cattgccgcc	300
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141

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                                                                    120
tggagcgatc tgccaatttc caaacagtgg gagctatctt gttagcagtg gttggtgcaa
                                                                        180
ctgtggtctg ggcagcctcc ctggtgagcc cagagagtct ctgcaggtaa gcggtataga
                                                                        240
aggacetgga ttecatgage aeggggaete gggagaegga gecatteegg aacageaggt.
                                                                        300
                                                                        360
agcaagaggg gaagteggtg acaccaaact tteteaceae attggeetet gtgtteagea
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ccctgcgcac cgccacncct ttgtgctggg a
      <210> 433
      <211> 420
      <212> DNA
      <213> Homo sapien
    <220>
      <221> misc_feature
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      <223> n = A, T, C or G
      <400> 433
ctgtagcttc tgtgggactt ccactgctca ggcgtcaggc tcagatagct gctggctgcg
                                                                         60
tacttgttgt tgctttgttt ggagggtgtg gtggtctcca ctcccgcctt gacggggctg
                                                                        120
ctatctqcct tccaqqccac tgtcacqqct cccqqqtaga agtcacttat gagacacacc
                                                                        180
                                                                        240
aqtqtggcct tgttggcttg aagctcctca gaggagggcg ggaacagagt gaccgagggg
gcagcettgg getgaegtag gaeggttagt ttggneeete egeegaatge egeantteta
                                                                        300
                                                                        360
ctgtcccaca cctgacagta atagtcancc tcatcttcgg cttgggctct gctgatggtc
```

```
agggtggccc gtgntccccg agttggagcc agggaatene teagggatee canaggeen
                                                                        420
      <210> 434
      <211> 239
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(239)
      <223> n = A,T,C or G
      <400> 434
ccaaccanga gagaagggat cgcctggtgc ccagggccca ccaggagctc caggcccact
                                                                         60
tgggattgct gggatcactg gagcacgggg tcttgcagga ccaccaggca tgccaggtcc
                                                                        120
taggggaage cetggeeete agggtgteaa gggtgaaagt gggaaaceag gagetaacqq
                                                                        180
teteagtgga gaacgtggne eccetggace ceagggtett cetggtetgg etggtneag
                                                                        239
      <210> 435
      <211> 415
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(415)
      \langle 223 \rangle n = A,T,C or G
      <400> 435
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                                                                        60
tatgtatgtg gaatccanaa ctcagtgagt gcaaaccgca gtgacccagt caccctggat
                                                                       120
gtcctctatg ggccggacac ccccatcatt tcccccccag actcgtctta cctttcggga
                                                                       180
gcaaacctca acctctcctg ccactcggcc tctaacccat ccccncanta ttcttgqcqt
                                                                       240
atcaatggga taccgcagca acacacacaa gttctnttta tcgccaaaat cacgccaaat
                                                                       300
aataacggga cctatgcctg tttagggntn taacttggnt actggccgca anaattccat
                                                                       360
agtcaagagc atcacagnet etgeatntgg aactteteet ggetnteaga eetgn
                                                                       415
      <210> 436
      <211> 152
      <212> DNA
      <213> Homo sapien
      <400> 436
ccaggattga caggccatcc attcacagcc aggagatgct gggccagtcc ctccaagagg .
                                                                        60
teteegteat ggeagtgatg aaaacetaae agggtggeee cetgtgeeag eteaggtgae
                                                                       120
tggagcccga gggcctgaca ggttcccagc ag
                                                                       152
      <210> 437
     <211> 174
      <212> DNA
      <213> Homo sapien
      <400> 437
ccaggtactg gcacatcatg ctctggatgg gggtggtggt gtcctgtaag cagagaaaca
                                                                        60
ggaaattgtc gtagtcagta tcgagcagct gtggcctcgt tcgccaccgt atagttgatc
                                                                       120
```

```
ttgaacttct ttggattctc agtcttctct ccaaggacct tcttctcaac acag
                                                                        174
      <210> 438
      <211> 485
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(485)
      <223> n = A, T, C \text{ or } G
      <400> 438
                                                                         60
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gggctctcta ctatgacttg atcagcagcc cagacatcca tggtacctat aaggagctcc
                                                                        120
ttgacacggt caccgcccc cagaagaacc tcaagagtgc ctcccggatc gtctttgaga
                                                                        180
agaagctgcg cataaaatcc agctttgtgg cacctctgga aaagtcatat gggaccaggc
                                                                        240
                                                                        300
ccagagtcct gacgggcaac cctcgcttgg acctgcaaga gatcaacaac tgggtgcagg
cgcagatgaa agggaagctc gccnggtcca caaaggaaat tcccgatgag atcagcattc
                                                                        360
                                                                         420
teettetegg ngtggegeae tteaagggge agngggtaae aaagtttgae tneagaaang
acttccctcg aggatttcta cttggatgaa gagaggaccg tgagggtccc catgatgtcg
                                                                         480
                                                                         485
gaccc
      <210> 439
      <211> 317
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(317)
      <223> n = A, T, C \text{ or } G
      <400> 439
                                                                         60
gggccgtctt cccctccatc gtggggcgcc ccaggcacca gggcagtgat ggtgggcatg
                                                                        120
ggtcagaagg attcctatgt gggcgacgag gcccagagca agagaggcat cctcaccctg
                                                                        180
aagtacccca tcgagcacgg catcgncacc aactgggacg acatggagaa aatctggcac
                                                                        240
cacaccttct acaatgagct gcgtgtggct cccgaggagc accccgtgct gctgaccgag
gccccctga accccaaggc caaccgcnag aagatgaccc agatcatgtt tgagaccttc
                                                                        300
                                                                         317
agcaccccag ccatgta
      <210> 440
      <211> 338
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(338)
      \langle 223 \rangle n = A,T,C or G
      <400> 440
                                                                         60
ccanaaagac ttcccaggga agatgcttgg ctctctgctc caaggtgggc catggtatag
                                                                        120
ggccctcgaa gggcttgtgg ctggggtgat cccagggggc attgctcaaa gtgcacagga
ggtggcagca gggtcaggcg agttcctgtt ccagggacat caggagggag ggtagaagcc
                                                                        180
```

```
tagggagtgt gcgaggctgc tgggatgagg gagctcaggg gctaccagct aaccagcctc
                                                                        240
agctcaatgg tttctccatc cttgggtctg tagtcagcaa taccttgcaa cagtggggtg
                                                                        300
ttggggtctc ggagaagctg ccagaactcc ctttctcc
                                                                        338
      <210> 441
      <211> 505
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(505)
      <223> n = A, T, C or G
      <400> 441
ccacacagan tcaccaagcc acagacttgt cttccacaag cacgttctta tcttagccac
                                                                         60
gaagtgacca agccacacgt actaaaggtt gaactcaaag atatgtacag ggtattaaac
                                                                        120
aaataccaaq qqqaacaqtt aacttcaata caaqqtcqaa atcaqcaaca aqttctacaa
                                                                        180
tccagngctg atatcagata caagcttcaa ggacaatttc ttttcgaagg cttattccag
                                                                        240
tttcgngagg ctagcatgag gtgtgtgcat ttgccagggg caaatttcta ttctcaatta
                                                                        300
accoatgoag caaatgotac noatggtgon gagtoogttt agaagcattt goggtggacq
                                                                        360
atggagggc ccgactcgtc ttactcctgc ttgctaatcc acnngngctg gaaggnqqac
                                                                        420
agtgaggcca cggatggagc caccnatcca caccqagtnc ttqcqctctq qqqqtqcqat
                                                                        480
nathttgatc ttcatggtgc tgggc
                                                                        505
      <210> 442
      <211> 386
     <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(386)
      <223> n = A, T, C or G
      <400> 442
cgccaggtga tacctccgcc ggtgacccag gggctctgcg acacaaggag tctgcatgtc
                                                                        60
taagtgctag acatgctcag ctttgtggat acgcggactt tgttgctgct tgcagtaacc
                                                                        120
ttatgcctag caacatgcca atctttacaa gaggaaaccg taagaaaggg cccagccgga
                                                                       180
gatagaggac cacgtggaga aaggggtcca ccaggccccc caggcaqaqa tqqtqaaqat
                                                                       240
ggtcccacag gccctcctgg tccacctggt cctcctggcc cccctqqtct cqatqqaac
                                                                       300
tttgctgctc agtatgatgg aaaaggaggg nggacttggc cctggaccaa tgggcttaat
                                                                       360
gggacctana ggcccacctg gtgcag
                                                                       386
      <210> 443
      <211> 404
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(404)
      \langle 223 \rangle n = A,T,C or G
      <400> 443
```

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cctccctctc agagcttgcc ccagggactc tctggccctc agggttcaat gtattctgac
                                                                         60
caaggccaag ctttcctqqq qctcaggqaa aatcacactt tgctacccqa agctgtatcc
                                                                        120
cetcagatge caggaaggee gtgateatet gaeteeacee teetgagaea cattetetee
                                                                        180
ctgactgtcc tgttctaagt cagcggagca ccttaggatg gaggggtgga ggcgaggcca
                                                                        240
ngatgcagcc tetgtgaaca ggtgeetgga ggetgggaaa tgaeeetgag agggeaggae
                                                                        300
acagenaceg ngggettaag gtgagggngg agageaagnt tggeecaett tacaatteta
                                                                        360
gntcagagcc ancecetaac atggngggca tttattcatt tegg
                                                                        404
      <210> 444
      <211> 318
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(318)
      <223> n = A, T, C \text{ or } G
      <400> 444
catgggctat agtgcgctat gttgatctgg tgttcatgct aagttccgca tcaatatngc
                                                                         60
gactteting gagtggggga ccaccangtt gcctaaggag gggtgaacct gcctacgttg
                                                                        120
gaaatagagc tggtcaaaac tcctgtgctc atcagtagta gaattgcacc tgtgaatagc
                                                                        180
caccgcctc cagcntgggc aacatagcaa gaccctgcct cttaagataa aaattggaaa
                                                                        240
                                                                        300
acactggtan gaaaaaaagg ctgtttggtc taaanaagtc tggatngggt ataaatgaca
                                                                        318
cnaanctatc atgactnt
      <210> 445
      <211> 41.8
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(418)
      <223> n = A, T, C or G
      <400> 445
ccaqtccaac ctqctcctca ttattqtata aatgagcaga atcaatatgg cggaagccag
                                                                         60
cttcaattgc caatttggtg gcctctaaag ctttactttt aggaacctct gcaggcgcat
                                                                        120
aggtgccaaa tcccaggaca ggcatgaagt gaccatcatt cagcttcaca cactgatatt
                                                                        180
                                                                        240
togaatocat ttotgtoact agootggotg goaaatgttt otttottoot cootcacagg
ctataagagc aatgagctgg caacgcccct gagcacactg tctgctgntt aaccaatggc
                                                                        300
atgtgagagg agggacagag gcagtcttac acaagctgtg ataaaaattg catncagttc
                                                                        360
aaccagtttc ttacnttatt ctaatgngna ggaagtgtgn gaagagcaca aagtcaga
                                                                        418
      <210> 446
      <211> 361
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(361)
      <223> n = A, T, C \text{ or } G
```

```
<400> 446
ctgtccaatn acaacaggac cctcactcta ctcagtgtca caaggaatga tgtaggaccc
                                                                          60
 tatgagtgtg gaatccanaa cgaattaant gttgaccaca gcgacccagt catcctgaat
                                                                         120
gtcctctatg gcccagacga ccccaccntt tccccctcat acacctatta ccgtccaggg
                                                                         180
gtgaacctca genteteetg neatgeagee tetaacceae etgeacagta teettggetg
                                                                         240
attgatggga acntccagna acacnacaca agagctcttt atctccancn tnactganaa
                                                                         300
gaacagcgcg actctatncc ttccaggggg ggggggtggg gnntgnggac cttnccgggc
                                                                         360
С
                                                                         361
      <210> 447
      <211> 321
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(321)
      <223> n = A, T, C \text{ or } G
      <400> 447
ccagganant ggttccccaa aggggacctc acccgcccg agctctggag ccgctgacgc
                                                                         60
tcgcatccag gacatttgag atgggaatcc aaataggcta cttgnaaaag acgtgctgca
                                                                       . 120
ngcagecetg gagagaetea tggagtteat tgtacattae tecatetaee gaggeagege
                                                                         180
atggcatgac tnaacggctt gnaacaaaca canaaattac caccacaaac attcaggaac
                                                                        240
caaatataat ctgctatggt cacaccacag acaatgcagg aagaggcttt ttattgctng
                                                                        300 -
ngtgngtttt caaatcatgt t
                                                                        321
      <210> 448
      <211> 325
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(325)
      \langle 223 \rangle n = A,T,C or G
      <400> 448
ccagcttcaa ctttttagta tagaagatac aggatcacaa aaaggagact acgctttgca
                                                                         60
aacatagcat caaaattcaa cttttctctt tgcagtttat ccatggngtc agcatacctt
                                                                        120
gcaagggaag ctacttacat caaataactt ttctatatac atttcctcat tgaccttttc
                                                                        180
tcaaagaata tcttggtttt gccgaacaaa cataatatag gngtctgcca gatccattcc
                                                                        240
tggtttctgt ngtgaaggaa aagcaggggg aacaaaataa tatcagggtc tcaatngtga
                                                                        300
nattattatt taatcatacc ctgan
                                                                        325
      <210> 449
      <211> 123
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(123)
      <223> n = A, T, C or G
```

```
<400> 449
cattaatntt ggaagcgatg gtgtggatta catcagtgtt agggcatggt gtggatatta
                                                                     60
ttacattann attggaagcg atggtgtgga ttacatcagt gatagggcac ggtgtggata
                                                                     120
                                                                     123
     <210> 450
     <211> 328
      <212> DNA
     <213> Homo sapien
     <220>
     <221> misc feature
     <222> (1)...(328)
      <223> n = A,T,C or G
      <400> 450
                                                                     60
ctggcaattt tgagctgccg gttatacacc aaaatgttct gttcagtacc tagctctgct
cttttatatt gctttaaatt tttaaagaaa ttatattgca tggatgtggt tatttgtgca
                                                                     120
tattttttaa caatgcccaa tctgtatgaa taatgtaaac ttcgattttt ttttaaaaaa
                                                                     180
240
ngggatgttt ttgtaangtt aattttctaa gactttttca catccaaagt gatgctttgc
                                                                     300
                                                                     328
tttgggtttt aactgtttca acntnggn
     <210> 451
      <211> 209
     <212> DNA
     <213> Homo sapien
      <400> 451
ctgccttgtt tcaacagaca tgcaaagatc ctaggagaca gtccccatag accttcagac
                                                                     60
attaaaaagg gagccgtaca gtttgtttga agcacttcgt cttacccatt tatgcagggg
                                                                     120
ccccaggaaa cttacacaca gccagaatga ggttcccaaa ggacttacat taattatggc
                                                                     180
tcttgcttcc tttcacaaat gagctgagg
                                                                     209
     <210> 452
     <211> 457
     <212> DNA
     <213> Homo sapien
     <220>
     <221> misc_feature
     <222> (1)...(457)
     <223> n = A, T, C \text{ or } G
     <400> 452
                                                                     60
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agcaaaatca agttcttttt gaaattttat cagtaatcca gaatttagta gtccatgcct
                                                                    120
totcactcag catttagaaa taaaaatgtg gtttcttaaa cgtatatcct ttcatgtata
                                                                    180
tttccacatt tttgtgcttg gatataagat gtatttcttg tagtgaagtt gttttgtaat
                                                                    240
ctactttqta tacattctaa ttatattatt tttctatgta ttttaaatgn atatggctgt
                                                                    300
ttaatctttg aagcattttg ggcttaagat tgccagcacc acacatcaga tgcagtcatt
                                                                    360
gttgctatca gtgtggaatc tgatagagtc tngactccgg ccacttggag ttgtgnactc
                                                                    420
                                                                    457
caaagctaag gacagtgatg aggaagatgg catgtgg
```

```
<211> 277
      <212> DNA
      <213> Homo sapien
      <400> 453
ccaattgatt tgatggtaag ggagggatcg ttgacctcgt ctgttatgta aaggatgcgt
                                                                         60
agggatggga gggcgatgag gactaggatg atggcgggca ggatagttca gacggtttct
                                                                        120
atttcctgag cgtctgagat gttagtatta gttagttttg ttgtgagtgt taggaaaagg
                                                                        180
gcatacagga ctaggaagca gataaggaaa atgactacga gggcgtgatc atgaaaggtg
                                                                        240
ataagctctt ctatgatagg ggaagtagcg tcttgta
                                                                        277
      <210> 454
      <211> 198
      <212> DNA
      <213> Homo sapien
      <400> 454
gttaaaagat agtaggggga tgatgctaat aatcaggctg tgggtggttg tgttgattca
                                                                         60
aattatgtgt tttttggaga gtcatgtcag tggtagtaat ataattgttg ggacgattag
                                                                        120
ttttagcatt ggagtaggtt taggttatgt acgtagtcta ggccatatgt gttggagatt
                                                                        180
gagactagta gggctagg
                                                                        198
      <210> 455
      <211> 608
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(608)
      <223> n = A, T, C \text{ or } G
      <400> 455
ctgagcaagc taaggaccag gggcaactag accctaataa tgngtacttt tgaaaatgat
                                                                         60
acaaactacc ttggttgtaa gaagtgcagg ttgaacactt taggagaaca gtcttcaaac
                                                                        120
tggcaattca aaatttccca ttatatgtga ataaaattgg aaggatgtta aatgtccatg
                                                                        180
gaaagttact cttgtaagtt aggatgcctt atactgaggc tttanaatga aagtacactt
                                                                        240
cacaaatgga atagtgaaca taaattacca gaagtcaaga taatagtcat actagtaagg
                                                                        300
taagcaaggt aaattccctt atacacaaaa attattttga tgaccttttt caataatgaa
                                                                        360
tctgaaatga agtgttttaa aaagctccct aaacacaaaa cgaacataaa actgcttaat
                                                                        420
aactttagag ctcatgtaat attcttgctg aaaacagtta ctgaaattac cagcgaaatg
                                                                        480
atggaatate tttaaageag gneactengt ataatetgga ataattteat ttgetaactt
                                                                        540
ttaagaagta ttctctggac tataaatcnt gggcaaatag acttccactt tattattacc
                                                                        600
ccaaatta
                                                                        608
      <210> 456
      <211> 467
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(467)
      <223> n = A, T, C \text{ or } G
```

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<400> 456 cctggacctg tgtaaacctt caaacactct tttttacatt aggtcgtgaa gttaaatttt 60 ttactgtttc tqtqctacag actcttcaaa gggaaatagt taagtcaatt tcaaagaaaa 120 tgaccagcac atttttaaaa cattagaaat gatttgactt tgactatcta ctgccaaaaa 180 aaggttaagg aatttgtaat gagaagctaa aaactttaag gaattttaag gaactcaaaa 240 caaaaactca ttaaatqtaa ttaaaqtqaa ttctacaaat aaagcctctt aatacatttc 300 tataatagtc acttaagact taaattcaaa cactagcaaa ccacaaaatc agactgtntg 360 actgacatcc aaaaqataaa tataaatcaa aatccgaccc cagcattagc caaggggtag 420 467 gtgttcctct tgaggaaggc aggaattcct cttctgccac ctgttgg <210> 457 <211> 183 <212> DNA <213> Homo sapien <220> <221> misc feature <222> (1) ... (183) <223> n = A, T, C or G<400> 457 ccaaattttn tactttaaac actgaaaaca gaggaagtta ataaaaattt taacctataa 60 120 aqtcccctgg ttgttagtca ttaacagcag attgtcagat aagactggta aaatgatggc tgctaagcat ttgatgatcc aggcgcagga tgatcaaact gcagcagatc atgcacgtga 180 183 cag <210> 458 <211> 445 <212> DNA <213> Homo sapien <220> <221> misc_feature <222> (1)...(445) <223> n = A, T, C or G<400> 458 60 qaaaaatata aagccaaaaa ttggataaaa tagcactgaa aaaatgagga aattattggt aaccaattta ttttaaaagc ccatcaattt aatttctggt ggtgcagaag ttagaaggta 120 aagcttgaga agatgagggt gtttacgtag accagaacca atttagaaga atacttgaag 180 ctagaagggg aagttggtta aaaatcacat caaaaagcta ctaaaaggac tggtgtaatt 240 taaaaaaaac taaggcagaa ggtttttgga agagttagaa gaatttggaa ggccttaaat 300 ataqtaqctt aqtttqaaaa atqngaaqqa ctttcqtaac qqaaqtaatt caagatcaag 360 420 agtaattacc ancttaatgt ttttggcntt ggactntgag ttaagattat tttttaaatc ctgaggacta ncattaatgg gacag 445 <210> 459 <211> 426 <212> DNA <213> Homo sapien <220> <221> misc feature <222> (1)...(426) <223> n = A,T,C or G

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<400> 459
cctatgatan cttctctagc tatcatactc caatcagcaa aaaatgagaa aatgttqaga
                                                                         60
aatagaagat aattootoat ttaaggooac ottotagaat ttgtgottaa qattotqott
                                                                        120
tcttctcatg ggccagcact tcggcaactg gcaaaaatta ggtgtacagg gatctaggta
                                                                        180
atactgttta tttgagcaat aatatattgt gctaacgttc aggcatccta ttactgagaa
                                                                        240
ataagggaaa atgagtgtaa agtacaacta agagtctcgg cgacagggaa aaataccatc
                                                                        300
agttaaatat ccatagtcct agagcattta tqtaaaactq caatntqaat cctqcaatac
                                                                        360
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gataga
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agtttggtta tatttcactg aaaattttct tccagagtag gttttttttc gtgggttggg
                                                                        120
gggtaacttt actacaatta gtaagtntgg tgcagaattt catgcaaatg aggagtgcag
                                                                        180
cagngtgata atttaaacat atntaaacaa aaacaaaaaa aatgaatgca caaacttqct
                                                                        240
gctgcttaga tcactgcagc ttctaggacc cggtttcttt tactgatnta aaancaaaac
                                                                        300
aaaaaaanta annachttgt geetgaaatg aanettgttt ttttntna
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      <210> 461
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      <212> DNA
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      <223> n = A, T, C \text{ or } G
      <400> 461
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                                                                         60
catggtgagc agtggtcaat ctgtgccctg tggaatgatg ggcaqataat tctggcatgt
                                                                        120
gtaaataata ataaataatt cacttggtgc aggcagtatg tctatgaatt aaaacctagt
                                                                        180
gtgtacacag tgcctacatg tgttacagcc ccacagtagg aatctacacc aaaatattta
                                                                        240
ttagaaggaa tttggtccgt actacatcac gctttccgga gggtaaaaaa taaagtccat
                                                                        300
ctatagacat ttcaccacag acccagagac tgagtctggc taaaacctgc aaaatgtcta
                                                                        360
taacaaaagn qqatqqct
                                                                        378
      <210> 462
      <211> 197
      <212> DNA
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      <220>
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<222> (1)...(197)
      <223> n = A, T, C \text{ or } G
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catttggagt gngcagcaca nttacttcat gttgctcang tttanaacaa tntcccctgn
                                                                         120
aagttctcac acagatnggn agaaatcata cctanttntg gtnaatcact atggcagccg
                                                                         180
tngaagaatn taagaga
                                                                         197
      <210> 463
      <211> 279
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(279)
      <223> n = A, T, C \text{ or } G
      <400> 463
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tgcacatata catgttcaca gcatgtatac aatgataatc cctacggttt aaccaagtta
                                                                         120
tqqttccctt ctacaqcaqa cacaaaacca aggtgaacta ggtnggcaga tgtanaggga
                                                                         180
ataccaaaaa aagggtaatn ngntcactga ttctgaagna tntgactgan catactgagc
                                                                         240
                                                                         279
ttctgnactt tgggaatgca tnnaggnaac aatatcttg
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      <211> 552
      <212> DNA
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      <400> 464
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                                                                         60
                                                                        120
acateetgea caggtactee aaaactaaaa gtaaaaaaat etaaaagaaa aaagaaaaaag
aattaaaccc aaaatcactt ccccatctgg acttgattta gatgaaaagc ttctggactt
                                                                        180
                                                                        240
tgagctgatg ctatagtggg ttgaaaattt tggggtcctc agaaggggat gaggatatat
tgcatgagag agcaacatga atcatngaga gccagagtat agagagnggt gggtagactg
                                                                        300
taggagagec eteaatgate eeggetgtet tgtattegeg ttgeaettae ttgtataata
                                                                        360
                                                                        420
tggcagatgg gatgtgatgt cactttcaag attangttat aaatagacta tggcttcaat
caqaggqttt tcttctctgt ctanctctct tttgggtagn ttcattctga gagaaagcca
                                                                        480
nacetengee genaceeaeg etaaggggeg antteeagen eaetggegge engttaetag
                                                                        540
tggatccgng ct
                                                                        552
      <210> 465
      <211> 444
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
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<222> (1) ... (444)
      <223> n = A, T, C or G
      <400> 465
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acagttctgt ttatgagctt cagctactga taaagcactt cctgaacttc tctattatca
                                                                        120
tagngaccct ctgaataacc tgagtgactg gctcggcaat tcgctttata accattctta
                                                                        180
ttcccaaagt tggagcacat aaacatttag atgtcttttc ctgtaaaata ttctagacat
                                                                        240
ttacccaaac tctaqttcaa catatactca acttqcactg tatatctccc tgcttttttq
                                                                        300
agacagagaa gaaattcagg aggtgnccca tctccagagt ttctctgttg gaaagcagcn
                                                                        360
atcaagaanc ctttaaaaaa ttggtgtnaa gctntgccnc ctgcagaaat gcntngcccc
                                                                        420
acattattct tctggggnaa agna
                                                                        444
      <210> 466
      <211> 381
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      <221> misc_feature
      <222> (1)...(381)
      <223> n = A, T, C \text{ or } G
      <400> 466
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ctgttcctct ttggactaac agttaaattt acaaggggat ttagagggtt ctgtgggcaa
                                                                        120
atttaaagtt gaactaagat tctatcttgg acaaccagct atcaccaggc tcggtaggtt
                                                                        180
tgtcgcctct acctataaat cttcccacta ttttgctaca tagacgggtg tgctctttta
                                                                        240
gctgttctta ggtagctcgt ctggnttcgg gggtcttagc tttggctctc cttgcaaagt
                                                                        300
tatttctagt taattcatta tgcannaggt ataggggnta gtccttgcta tattatgctt
                                                                        360
qqttataatt tttcatcttt c
                                                                        381
      <210> 467
      <211> 95
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(95)
      <223> n = A, T, C or G
      <400> 467
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                                                                         60
                                                                         95
qaqctqaanc caangancqc caataataat acttt
      <210> 468
      <211> 224
      <212> DNA
      <213> Homo sapien
      <400> 468
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                                                                         60
aaaaatcata tgtacttatt tgaaggtaaa gattattcta aagagcccag taaggaagac
                                                                        120
                                                                        180
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gagggccgat cactccqaaa taaaggcagt gttctcatcc cagg 224 <210> 469 <211> 416 <212> DNA <213> Homo sapien <400> 469 60 ctgagttcta gttcaaaagc tttatcctta acttcgtcat gtactatgta aattctagaa tagaaaaggg aaaggtaaga ttttggtaac ctccaaacat tgaagtagtt cacagaccca 120 aagtcagtac aaattagaat gtccatccat aataaaagta tctataaaaat tacacagaca 180 cattctacat aqtatttaac attagagaag acaaattaca cagggactga aataaaatga 240 aacatctact ctcccqacaa atqttqaata tacctaatca acccaagttc agtttatttt 300 tgcacattgc tttagagata taacttggct gggcacagtg gctcacacct gtaatcccaa 360 cactttggga gaccaaggcg gatggatcac ttgaggtcag ttcgagacta gcctgg 416 <210> 470 <211> 376 <212> DNA <213> Homo sapien <400> 470 caccttttaa ctgtatcaca aagtctgttg ctgtggttac agcctttgtt tccagtgatg 60 ttttgtccat gctttccccc aacccttaac aatggttact caaaagaatg aaataatgag 120 tcattcattc gggaatatgt taaaatatcc ctctttatca ttacatttca ctgcttayaa 180 actaggctgt aattcaaggc aacagttaag tctgagaact gttaaaaaaa tctttgattt 240 tttttcattt ttaaqaaaaa cctqcctatt taattqttca gacttgtaag aggttcttca 300 attacatcct ttttggttaa tgtattattt ctggaacaag tagataaaat tctacgcagt 360 aagcataata aaaatc 376 <210> 471 <211> 357 <212> DNA <213> Homo sapien <400> 471 ggcttcgtat aatggttctt ttgtcacccc tgatcgacga tttcgctacc cgtacaactc 60 tgacaaggga acgaaatgct tctgtgtatt cacctagtgg tcctgtgaac agaagaacaa 120 caactccacc ggatagtgga gtactgtttg aagggttagg catttcaaca agacctagag 180 atgttgaaat tcctcagttt atgagacaga ttgcagtaag gaggccaact acggcagatg 240 aaagatcttt gcggaaaatt caagaacaag atattattaa ttttagacga actctttacc 300 gtgctggtgc tcgagttaga aatattgaag atggtggccg ctacagggat atttcag 357 <210> 472 <211> 557 <212> DNA <213> Homo sapien <220> <221> misc feature <222> (1)...(557) <223> n = A,T,C or G<400> 472 60 cngagatgac atttacaatc tcttgaaang cagcagatgg cactctggtg cttcctatga

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cacctacgtt taccaaaaaa gctgacatct caaactctga gttgttgaga ctcaaatttc	180
tcatccccaa agaagcctat tacggtagtg tgntggatgc tttttgtatc tctgataggc	240
aggcactata atggggggaa atacttctga ataaaaacat tggctgtctt gcaactgtgc	300
atataatgtc tattcaaggg ggcagtgtgc ctagcatgat cctgaaatgt tgagataaaa	360
ggaagttggc attaaagcac tatttgtctt atatgaaaag agtgactcta tcttccagta	420
aacaagantt cctgcaatga aaaagaaatt ttttccttca ttatctataa actatacaaa	480
ataaccttcc tttttaacct aagactcaaa cattnatatt tgattttatt ctatttgata	540
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100 100	
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acagttgtca gacaaagccc tcgaaggatt aagccagtta ggattattcc ttcttcaaaa	180
aggacagatg caaccattgc taagcaactc ttacagaggg caaaaaaggg ggctcaaaag	240
aaaattgaaa aagaagcagc tcag	264
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ctttacatca tacttggaca tatcaagcat tggtgcacga tgtactggat ttccatttaa	120
acagggttaa tttggaagaa tcttcaggag tggaaaactc tccag	165
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against at a sagarant and the description of the transfer of the sagarant and the sagarant	120
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aaaataaaac tggacagcat tccacatcca agtgcacaga accatttttg caagattaaa	180
	-
aaaataaaac tggacagcat tccacatcca agtgcacaga accatttttg caagattaaa	180
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aaaataaaac tggacagcat tccacatcca agtgcacaga accatttttg caagattaaa taatgtaaac attgggaaca gccaaatcag cgaagaatgc caacacctca aaacacctgg tgttgccgct tcattaagtg gttcaaaatc cagatctata attgcgcaat attcaccgta	180 240 300 360
aaaataaaac tggacagcat tccacatcca agtgcacaga accatttttg caagattaaa taatgtaaac attgggaaca gccaaatcag cgaagaatgc caacacctca aaacacctgg tgttgccgct tcattaagtg gttcaaaatc cagatctata attgcgcaat attcaccgta tataaaaaga aatggatatt aattttgaca aatagctgca actgagactt ctttttattt	180 240 300 360
aaaataaaac tggacagcat tccacatcca agtgcacaga accatttttg caagattaaa taatgtaaac attgggaaca gccaaatcag cgaagaatgc caacacctca aaacacctgg tgttgccgct tcattaagtg gttcaaaatc cagatctata attgcgcaat attcaccgta tataaaaaga aatggatatt aattttgaca aatagctgca actgagactt ctttttattt ctttatatgn gnatatagtg aatttttatt atttttaaaa ttttattat tttttta	180 240 300 360

<212> DNA

<213> Homo sapien

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<220>
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      <222> (1)...(321)
      <223> n = A, T, C \text{ or } G
      <400> 476
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aatgtqcaaa tacactttaa aatqcangtt attctatagc anttgcaaga tagaatttca
                                                                         120
ctgtaattag ggaatctagc tcatcctaac ttaatagnct tttgcatgtn tagacaatgc
                                                                         180
aattctacaa ggnacnactc agcgttgatg ctaaagtatg aaacacatcc tcagattatt
                                                                         240
catccgaaaa tattaaaata gcntcatgtt ttattattct ttaatgagtc ntgagctcat
                                                                         300
ttctaaagct tcataaagca t
                                                                         321
      <210> 477
      <211> 546
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
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      <223> n = A, T, C \text{ or } G
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                                                                         120
gcaccettca tteetgtagt etcacaggaa gtgttgetga ggagaetttg ggetgeaegg
                                                                         180
tacatgagtt tcttgcaatg acaaatgaac agaaaacagc attaaagtgg caattcctct
                                                                         240.
                                                                         300
tggaaagaag caaaatttat ttaaaattcg ttctatcaca cagagcaagg agtggattga
aaattagtgt actotogtgo aagottgoag atootactga ggcaagcaga aacttgtotg
                                                                         360
                                                                         420
gacaaagaca tgtttaaaac ggtctatcat tttgaactct ggaaaagtat aagagtttta
actcccttta aaatggaata ttaatttgaa aattatgggg aaaattgcat tttgtttaca
                                                                         480
tgtggtgaac atgtttctag aaattggtat ggcgggaagg gggctgggtg agtctgaagg
                                                                        540
                                                                         546
acctcn
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      <211> 100
      <212> DNA
      <213> Homo sapien
      <400> 478
                                                                          60
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gttgactttg attttgctgg acctgcaatc catggttcag
      <210> 479
      <211> 508
      <212> DNA
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      <220>
      <221> misc feature
      <222> (1)...(508)
      <223> n = A, T, C \text{ or } G
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tttcaagang qagaaatctg cttcataaat agnaggaatc tatgcttaaa ctnaacattt
                                                                        420
aatqqtqacn tcttacaaca qccttqaaaa nnattqqaan tcnqacntqa nqqnqqaaac
                                                                        480
tggaanaaag aatatettte tettetgeat eettinatee teaaaettag catggattea
                                                                        540
cacgctgagg aaangttngg tnacnaccng aacatttaga ta
                                                                        582
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      <211> 275
      <212> DNA
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      <220>
      <221> misc_feature
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gatttacaaa atagaacact ttaaaccagg tcagtcctat ctttttgtag ctgaaggcta
                                                                        120
tcagtcataa cacaatttcg cgtacacctc tgctcattat ggaattacac ttaaaacgaa
                                                                        180
tctcaagagg gtgaccattg ttgtttcaga taccatccct aaggagagtg gttaacagga
                                                                        240
                                                                        275
agattqccag ngttactqat ggaaaqaagc gcttg
      <210> 484
      <211> 434
      <212> DNA
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      <400> 484
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tttcctcttt gctttgttta ctcatgattg ccagatggct acgttacctc taagcatcag
                                                                        120
atcctcacaa attaatggtt aaatgtaagg gagggatttt actctcttgc attaaaaaaaa
                                                                        180
                                                                        240
agetttattg agatataatt tactgtaaca ttgactcatt taaagtatge tagtcaatag
accaaatctt gaataaactc ccattcacaa ttgctacaaa gggaataaaa tagctgggaa
                                                                        300
tatagctaac aagggaagtg aagggcctct tcaaggagaa ctacaaacca ctgctcaaga
                                                                        360
aataagagag gatacaaaca aatggaaaaa cattccatgc tcatgaatag gaagaatcaa
                                                                        420
                                                                        434
tatcgtgaaa atgg
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      <211> 291
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      <400> 485
                                                                        60
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taaqttttca cgcaatacac aaaaaacccc tctgcacttc ttgtaaagaa caaaaaagat
                                                                        120
acacaacagt taagcgtaaa gatcacaggc aatagcattc aaacatggat gtgggtagag
                                                                       180
aaaggagtac ctggcatgag tacctgctta gtttgactga atccttgatt tttaatttgg
                                                                       240
cttttcatgg gccgctcaca acaccaacgc tgtgtgaggt atggtagtca g
                                                                       291
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       <213> Homo sapien
       <400> 486
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gcacgctcag agacagtgaa ctagcatttg aatacacaag tccaagtcta ctgtgttgct
                                                                         120
aggggtgcag aacccgtttc tttgtatgag agaggtcaaa gggttggttt cctgggagaa
                                                                         180
attagttttg cattaaagta ggagtagtgc atgttttctt ctgttatccc cctgattgtt
                                                                         240
ctgtaactag ttgctctcat tttaatttca ctgg
                                                                         274
      <210> 487
      <211> 184
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(184)
      <223> n = A, T, C \text{ or } G
      <400> 487
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ccctgatatt tatacatgat attcgnaaaa tgtaaagaag ctattattca tacagacatc
                                                                        120
tagagaagga gngaagnttt taaaaaaaata aaaaaatact tatttcaagc tttagctgtg
                                                                        180
ttct
                                                                        184
      <210> 488
      <211> 393
      <212> DNA
      <213> Homo sapien
     <400> 488
ctgcattttt attgcgatct gcagatgaac tggaaaatct cattttacaa cagaactggg
                                                                         60
acagacgacc accatattca ctgaggtcta aatttgcagt ttccactaat gacattttga
                                                                        120
tttcccaaca gagatacttc tggtcttact gcacagtctt ttaagagaaa tacttccatt
                                                                        180
atgccacatt gtccttgatc cgtaagtgat gtgttaaggt gcttcaaagg aactctgacc
                                                                        240
tctgaagtac ttgagctact ttagtatgtc cagcctattg ctttttgttt tagtgtgtca
                                                                        300
ccataaatat caggggcata aaaggctatc tattcttaat tcaaggataa aacagaagaa
                                                                        360
gcttgtggta taaaacaata gttcaagatc cag
                                                                        393
      <210> 489
      <211> 607
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(607)
      <223> n = A,T,C \text{ or } G
      <400> 489
gtgcttatgt acttaagggg aactactcta actgggtgaa gagtangatg aagcatccat
                                                                         60
gtccctacaa aggatatgaa ctcatccttt tttatggctg catagtattc catqqtqtat
                                                                        120
atatgccaca ttttcttaat ccagtctatc atcgatggat atttgggttg gttccaagtc
                                                                        180
```

```
tttgctattg tgaatagtgt cgcaatgaac atacatgtgc atgtgtcttt atagcagcat
qatttataat cctttqqqta tatacccaqn aatgggatag ctgggtcaaa tggtatttct
                                                                         300
agttctagat ccttgtggaa ttgccacact gtcttccaca atggttgaac tagtttacag
                                                                         360
tcccaccaac agtgtaaaag tggtcctatt tctccacatc atctccagca cctgttggtt
                                                                         420
cctgactttt taatgattgn cattccaact ggtgtgagat ggtatatcac cgtgggtttg
                                                                         480
atttqcattt ccctqatqqc caqtqatqat qaacnttttt tcatqtqqtt tttqqctqca
                                                                         540
taaatggcct gccttttnta cttctataaa atttttcann tcttattatt attcctgggg
                                                                         600
gnttaag
                                                                         607
      <210> 490
      <211> 179
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(179)
      \langle 223 \rangle n = A,T,C or G
      <400> 490
cttctaggaa tactagtata tcgctcacac ctcatatcct ccctactatg cctagaagga
                                                                         60
ataatactat cactgntcat tatagctact cccataaccc tnaacaccca ctccctctta
                                                                         120
gccaatattg ngcctattgc catactagtc tttgccgcct gcgaagcanc ggtaggacc
                                                                        179
      <210> 491
      <211> 399
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(399)
      <223> n = A, T, C \text{ or } G
      <400> 491
cctctacctg taatcacatt aatttttcta aagacagggg nggtgttttg aagataaatg
                                                                         60
                                                                        120
tcattagtct atgataatag catcatagga caattagcca ttttagactt gaccatattt
tctcttttta qcatataqcc atcttqatat ttaqqnqqqa qactactcca atqqaqcaac
                                                                        180
agtttcattt tacatgattg gatttagaaa tttacaaatt ttaaactcat aagaattcta
                                                                        240
aataatttga aaatggaaac atttgaccca cagtctagca gcataaatac atttataaaa
                                                                        300
tacttcattg ttgatcttag gtcattgatt taaaacagaa tttggtgact atgggcaggt
                                                                        360
ggaggggcc ngtgaggaag gtataaaaga gaaatcttt
                                                                        399
      <210> 492
      <211> 482
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(482)
      \langle 223 \rangle n = A,T,C or G
      <400> 492
ctccacctta ctaccagaca gccttagcca aaccatttnc ccaaataaag tataggcgat
                                                                         60
```

```
agaaattgaa acctggcgca atagatatag taccgcaagg gaaagatgaa aaattataac
                                                                         120
caagcataat atagcaagga ctaaccccta taccttctgc ataatgaatt aactagaaat
                                                                         180
aactttgcaa ggggagccaa agctaagacc cccgaaacca gacgagctac ctaagaacag
                                                                         240
ctaaaagage acaccegtct atgtagcaaa atagtgggaa gatttatagg tagaggegae
                                                                         300
aaacctaccg agcctggtga tagctggttg tccaagataq aatcttagtt caactttaaa
                                                                         360
tttgcccaca gaaccctcta aatccccttg taaatttaac tgttagtcca aagaggaaca
                                                                         420
gctctttgga cactaggaaa aaaccttgta gagagagtaa aaaatttaac acccatagta
                                                                         480
gg
                                                                         482
      <210> 493
      <211> 207
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(207)
      \langle 223 \rangle n = A,T,C or G
      <400> 493
cataaatatt atactagcat ttaccatctc acttngngga atgctagtat atcgctcaca
                                                                          60
cctcatatcc tccctactat gcctagaagg aataatacta tcactgttca ttatagctac
                                                                         120
totcataaco otcaacacoo actooctott agocaatatt gtgootattg coatactagt
                                                                         180
ctttgccgcc tgcgaagcag cggtagg
                                                                         207
      <210> 494
      <211> 283
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(283)
      \langle 223 \rangle n = A,T,C or G
      <400> 494
ccaattgatt tgatggtaag ggagggatcg ttgacctngt ctgttatgta aaggatgcgt
                                                                          60
agggatggga gggcgatgag gactaggatg atggcgggca ggatagttca gacggtttct
                                                                         120
atttcctgag cgtctgagat gttagtatta gttagttttg ttgtgagtgt taggaaaagg
                                                                         180
gcatacagga ctaggaagca gataaggaaa atgactatga gggcgtgatc atgaaaggtg
                                                                        240
ataagctctt ctatgatagg ggaagtagcg tcttgtagac cta
                                                                        283
      <210> 495
      <211> 590
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(590)
      <223> n = A, T, C \text{ or } G
      <400> 495
tatgtatata attttcttag ttactagcat agagaaatta ctgatttaaa aaaacatttc
                                                                         60
aaattctagc atgttgtagg attctattgc cctttctaaa aagtacatct tgcttatccg
                                                                        120
```

164

```
atttctaaca aaactattta atttgaagaa gggagaatga atttggataa aaagcaaaaa
                                                                     180
tttaaaggta ctcaaattta ggcaaaccat taaagcaatc ttagtttaca gttaattggg
                                                                     240
tagaatggtc aacactttct tcaggttagt tcatggagtg gatatgcatt gatagaacaa
                                                                     300
cttagagatg cttttacagt tgagaaagct cattatattt gttatcttta agaatcagct
                                                                     360
tatttatttc atatgtttgt tctttaagaa gaccaaagag ccctgcaaat gaatgttgat
                                                                     420
ttgtttttt qtttgtttaa tatttttgta qagataagat ctcactttgt tatgttgccc
                                                                     480
aggotggtot caaactotca acttgaagtg atotgcccac ctcagcotco caaagtggtg
                                                                     540
ggattacagg catgagccac cgcacctgga cctgcccggg cggncgctcg
                                                                     590
      <210> 496
      <211> 307
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (307)
      <223> n = A,T,C or G
      <400> 496
ggagattagt atagagaggn anachttttt tcgngatatt tggtcacatg gataagtggc
                                                                     60
gctggcttgc catgattgtg aggggtagga gccaggtagt tagtattagg agggggnng
                                                                     120
ttagggggtc tgaggagaag gttggggaac agctnaatag gttgttngnt gatttggnta
                                                                     180
aaaaacanta gggggatgat nctaataatt antgctgtgg gtggttgtgn tgattcaaat
                                                                     240
tatgngcttt ttcggagann catgtcangt ggtagtaaat ataattgttg ggaccattan
                                                                     300
                                                                     307
      <210> 497
      <211> 216
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(216)
      <223> n = A, T, C or G
     <400> 497
cattttcctc ttqqtttctt caqttaaqtc aaannqncac qttcctcttt ccccatatat
                                                                     60
tcatatattt ttgctcgtta gtgtatttct tgagctgttt tcatgttgtt tatttcctgt
                                                                    120
180
concnaantt gaaaaaatqn ttntttttcc ctnaca
                                                                    216
      <210> 498
      <211> 375
      <212> DNA
     <213> Homo sapien
     <220>
     <221> misc_feature
     <222> (1)...(375)
     <223> n = A, T, C \text{ or } G
     <400> 498
```

gaatttcctg gcaccttttc tcgctagaga agattnngtg tgactgggtt gcctataagc

```
catatagata caaactttta tctctaatac caagtcttag agggatatat taatagatct
                                                                         120
aataaattta ttcttagact tattgtttca tgggntagtg agtctttgct actggagaca
                                                                         180
atacagactt gtcagttttt ttaaaaaaaa aaaatttgcc aagctancac attaaaaana
                                                                         240
tntcctaagg ctntcatttt atgaggatga ttataaacnt ttntgngata aatatcacca
                                                                         300
taataaactg ttaagtacaa ctgcnggccn cccttanagn gaattcctnc agttanaaat
                                                                         360
ttatttttt gccaa
                                                                         375
      <210> 499
       <211> 215
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(215)
      <223> n = A, T, C \text{ or } G
      <400> 499
ccacnaaagc agaagcttaa agcatagtag taaagaggnn aaaaagaagg acgaaaataa
                                                                         60
atcagatgac aaggatggta aagaagttga cagtagtcat gaaaaggcca gaggtaatag
                                                                        120
ttcactcatg gaaaagaaat taagtagaag gttgtgcgaa aatcggagag gaagcttgtc
                                                                        180
acaaaaaaa aaaaaaaaaa aaaaaaaaa gtttt
                                                                        215
      <210> 500
      <211> 489
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(489)
      <223> n = A, T, C \text{ or } G
      <400> 500
ccactacgat aagcaggtag ctgggttttg tagtgagntt gctccttaag ttacaggaac
                                                                         60
tctccttata atagacactt cattttccta gtccatccct catgaaaaat gactgaccac
                                                                        120
tgctgggcag caggagggat gatgaccaac taattcccaa accccagtct cattggtacc
                                                                        180
agccttgggg aaccacctac acttgagcca caattggttt tgaagtgcat ttacaaggnt
                                                                        240
tgtctacttt cagttcttta ctttttacat gctgacacat acatacactg cctaaataga
                                                                        300
tctctttcag aaacaatcct cagataacgc atagcaaaat ggagatggag acatgatttc
                                                                       360
tcatgcaaca gcttctctaa ttatacctta gaaatgttct cctttttatc atcaaatctg
                                                                        420
ctcaagaagg gctttttata gtagaataat atcagtggat gaaaacagct taacatttta
                                                                        480
ccatgctta
                                                                        489
      <210> 501
      <211> 286
      <212> DNA
      <213> Homo sapien
      <400> 501
aaaaacactc aaacacagcc ttggagggag gagtcagttt taaaaagactc ttataaaagt
                                                                        60
aatatactgc tagctctgaa gaatcggagg ctaaaatcat ctcttcaagt ccccagggaa
                                                                        120
tcccaaagaa ctccagggga aggtgggatg ggccagagag ctctggaagc ttccaggtct
                                                                        180
gttgcaagcc tcacctggta cacagtaggc tcttccaggt ctgtcaggaa cccaggagcc
                                                                        240
tcccctagca cacagtaggc tcacaaaaag ggagcactgc tgctgg
                                                                        286
```

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<220>

```
<210> 502
      <211> 168
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(168)
      <223> n = A,T,C or G
      <400> 502
cctatgattg tgggggcaat gaatgaagcg aacagagntt cgttcatttt ggttctcaga
                                                                         60
qtttqttata atttttatt tttatgggct ttggtgaggg aggtaagtgg tagtttgtgt
                                                                        120
                                                                        168
ttaatatttt tagttgggtg atgaggaata gtgtaaggag tatggggg
      <210> 503
      <211> 173
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(173)
      <223> n = A, T, C or G
      <400> 503
cctttataat aaattaggca aaaggttcag tgcnnggcta tantggacaa catgaaactc
                                                                         60
cataaaaatg actggatagg gggactgctt gagacttttc ttttgggcat tactaacaga
                                                                        .120
attcaaagaa attccaacca cgcttatttt tccaaattct actgaaatga gag
                                                                        173
      <210> 504
      <211> 310
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(310)
      <223> n = A, T, C \text{ or } G
      <400> 504
tagtattcta tttaaaaatt aagttttggg gtctgtaaaa tatacaggac aatgactttt
                                                                         60
ttaaaatgta agttaatacc tcctcctcac ttgtcttaat tgaacttagg tgtttattct
                                                                        120
taaaggngga ccttgatgaa aatgttgaga tgggaagtgt tattaggcaa aacttgttat
                                                                        180
agatttctca tataactctt aattgaccct tagaatttta acaaccgcgc ctggcccaat
                                                                        240
agactgtttt ttagagtant tttaggctct cancaaaatt gaggggaaaa tacagggtgt
                                                                        300
                                                                        310
tcccattaaa
      <210> 505
      <211> 530
      <212> DNA
      <213> Homo sapien
```

167

```
<221> misc feature
      <222> (1)...(530)
      <223> n = A.T.C or G
      <400> 505
cctcagggaa cttacaatta tggcaaaagg ggaaggggaa gcaagcacct tcttcacaag
                                                                         60 .
gcatcaggag agagagaa agagagtagg ggaaactacc ccttttaaac catcatatcc
                                                                        120
tgtgagaact ccctcagtat tagaagagca tgagggaaac cgcctccata atccaatcac
                                                                        180
ctcccaccag gaccatccct caatacatgg gggttacaat tcaagatgag gttcgggtgg
                                                                        240
ggatacagat ttaaaccata tcagaatggt taatgatatt gttgtatttt accaactata
                                                                        300
atcttcttag tgttatagta caataatgta aaaaattgag taaatttgtt ttctatatta
                                                                        360
ttctgttttt ggaaaacatg tatatagtca gggctgtttg tctcaagaaa atatggtaaa
                                                                        420
ctctgctgtt ttggtcactg gtgcctagaa tttggggatg tacattggtt ttgattcaca
                                                                        480
tgcacatttc cttctagttc acagtaacta tttctaacta tttcccnata
                                                                        530
      <210> 506
      <211> 352
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (352)
      <223> n = A, T, C \text{ or } G
      <400> 506
cttgaacgct ttcttaattg gtggctgctt ttaggcggta ctatgggtgn taaatttttt
                                                                        60
acteteteta caaggittit teetagigte caaagagetg ticetetiig gactaacagi
                                                                        120
taaatttaca aggggattta gagggttctg tgggcaaatt taaagttgaa ctaanattct
                                                                        180
atcttggaca accagetate accageteg gtaggtttgt egeetetace tataaatett
                                                                        240
cccactattt tgctacatag acgggtgtgc tcttttagct gttcttaggt agctcgtctg
                                                                       300 .
gtttcggggg tcttagcttt ggctctcctt gcaaanntat ttctagttaa tt
                                                                       352
      <210> 507
      <211> 370
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(370)
      <223> n = A, T, C \text{ or } G
      <400> 507
cctaactaga tcttatcaga atagggggga agggngtcgg ttcatcctta ttgagtgtta
                                                                        60
atgaccctgt aagatgtaat ttcttttatt tcattctgtt acctagaaaa tctatcacag
                                                                       120
ccttgtagta ttgattgctc aatctataaa gagctcagtt tacagcatga ctgttagtaa
                                                                       180
cagggntatt ttaatgagtg actetteaac aceteagagt tteactaaat tecaacecat
                                                                       240
cageccagta gtetaacatt aagggtetta ggaaatgaga aettateace ttteettate
                                                                       300
atqaaaaqqt aacctccaqq taaccaaaaa tagaacttcc tctqtgttcq ttttttataq
                                                                       360
aaattactgg
                                                                       370
      <210> 508
```

<211> 129

<212> DNA

```
<213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(129)
      \langle 223 \rangle n = A,T,C or G
      <400> 508
ctqttaaaaq aacaaactta gcaatatata acagttnggt aacaggattt ttgactattc
                                                                          60
actttgggag ttattttaa aaatccactt ttttactgag tcttactaca taccaggcac
                                                                          120
                                                                          129
tgtacttgg
      <210> 509
      <211> 422
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(422)
      \langle 223 \rangle n = A, T, C or G
      <400> 509
                                                                          60
ntgggaagtc gtgacatcca tgggaaccca gcgctgtgat gctggtgttt gngttctccg
cgagaagtga ccattgttgg agcaccatcc agagctagtg accantncag tggacagtta
                                                                          120
                                                                         180
qtqqqaqaat caaaaatcct ttccaqaatg tctgtttctc actacntgca ccgggngatt
acaggcacca gtgcagngat gattgtactt atttgacaca tactccccgt cntcctggnt
                                                                         240
                                                                         300
nttqttcctq anaanqqtqq qtaaatattc caggaaaaan aatgcacatt gaatggatgt
                                                                         360
gagagaccac attgcctctc ccactgcttt ggggagcact ttcctgtcat ttctaactta
                                                                         420
ccacntqctt qqtqtactat atqtatqttq tqcctcatat gttqcaaaqa actaanqtqa
                                                                         422
qt
      <210> 510
      <211> 238
      <212> DNA
      <213> Homo sapien
      <400> 510
ccacctatga attggtggtt tacctactca atggatagca gcacgaggac tgctgtactg
                                                                          60
cacaaaaaga agaccaaaag attacagtgg accatgggat acagaagcca gcatggcaga
                                                                         120
                                                                         180
cagaagaaaa atagtttggg aacatgtaac tatcctaagt ggaagttttg ttgtaggaat
tataqtaatc acaccacatt acttqqcctt tcggtaatgt gaaaaaaaaa aaaaatcc
                                                                         238
      <210> 511
      <211> 254
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(254)
      <223> n = A, T, C \text{ or } G
      <400> 511
conattgatt tgatggtaag ggagggatcg ttgnggctcg tctgttatgt aaaggatgcg
```

```
tacggatggg agggcgatga ggactaggat gatggcgggc aggatagttc agacggtttc
                                                                        120
tatttcctga gcgtctgaga tgttagtatt agttagtttt gttgtaagng ttaggaaaag
                                                                        180
ggcatacagg actaggaagc acgataagga aaatgactat gagggcgnga tcatgaaagg
                                                                        240
tgataagctc ttct
                                                                        254
      <210> 512
      <211> 269
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(269)
      <223> n = A,T,C or G
      <400> 512
cctacctgta aactacagta ctttatatat ctatgggntt aataaaaana aaatccacaa
                                                                         60
atcttaaaaa ggaactttaa atgcagggct atattgaatt ggnaaactgc aacacaaact
                                                                        120
ggcgcaacat aggtaaatga ataccaatct cactctatgt gatgcaagca tgctactttc
                                                                        180
ccactaattt aaattacttt caaccactat gagccagaat gcatgcctga accttaaact
                                                                        240
gcactttaaa aagtaacatc ttggcctaa
                                                                        269
      <210> 513
      <211> 266
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(266)
      <223> n = A, T, C or G
      <400> 513
ggagggggt tgttaggggg tcggaggaga aggntgggga acagctaaat aggttgttgt
                                                                         60
tgatttggtt aaaaaatant agggggatga tgctaataat taggctgtgg gtggttgtgt
                                                                        120
tgattcaaat tatgtgnttt ttggagagnc atgncantgg tagtaatata attgttgaga
                                                                        180
cgattagttt tagcattgga gtaggtttag gttatgnacc gtactctagg ccatatgtgt
                                                                        240
tgganattga nactagtagg gctagg
                                                                        266
      <210> 514
      <211> 271
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(271)
      <223> n = A, T, C \text{ or } G
      <400> 514
acatgcaana aatcgagaat cttaaaaaaac annacgaanc tgccctggaa nncttactgg
                                                                         60
nntangatat ttatnttgcg gctgagatac ttgaacaact tcggatcnga antagacaan
                                                                        120
aangggnant thtatactgc nncagaggtt acacagntca ttgtattaga gangaacana
                                                                        180
tgggtctggt gttcacacat tggggggaan atgggcgtnn acangagagg nnganaaacn
                                                                        240
anganageet neetggttng cataanaaaa a
                                                                        271
```

```
<210> 515
      <211> 328
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(328)
      <223> n = A, T, C \text{ or } G
      <400> 515
ccaatgaggg gcaaagtgag cgncnagaag angttttgac tgaaataaat caaacacaaa
                                                                         60
aatntaagtt cacagtgaca gtttaaacaa aatccaaaca aactaacaac anaaacaccc
                                                                        120
cttgntttgc ctctagtgga aggtgggana acacaanctc gtcctaaaaa ttgactagta
                                                                        180
aaggggaaaa cccggtcatt tncctactct ttccangaaa tatctaatgc aagaaagaac
                                                                        240
ttctnctcat tatacngaag gaatttngaa aaatgatgta tttttggaac acctaantga
                                                                        300
                                                                        328
aatactggaa cctgggcaag ttcaccac
      <210> 516
      <211> 220
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(220)
      <223> n = A, T, C \text{ or } G
      <400> 516
                                                                         60
ncctnagttg aaggacccca tgtacataca ggccagggga gcagtactag gntaactaga
aggateteat ecceatatgt gggeteattt caagtetatg gatgaetace tteattgntg
                                                                        120
                                                                        180
tgtgcgagat ggtttcaccc cttgaaaata tgggcacttc ancataanat agcnaaatct
                                                                        220
ttataatgat caatncatcc tacctccttt tacatgcatg
      <210> 517
      <211> 296
      <212> DNA
      <213> Homo sapien
      <400> 517
                                                                         60
tgcgatttct tccttgttgt ttgctttggt ctgtgttcaa tccagagagc ttaaattgtc
attattttgg gaagaaaacc tgtatttttg ttagtttaca atattatgaa atttcacttc
                                                                        120
aggagaaact gctgggcttc ctgtggcttt gttttcttag tttcttttc cgtgccgtgt
                                                                        180
                                                                        240
attititaat tgattitict tcttttactt gaaaagaaag tgttttattt tcaaatctgg
                                                                        296
tccatattta cattctagtt cagagccaag ccttaaactg tacagaattt ccactg
      <210> 518
      <211> 299
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(299)
```

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```
<223> n = A, T, C or G
      <400> 518
gaagatagaa aaatataaag ccaaaaattg gataanatag cactgaaaaa atgaqqaaat
                                                                      60
tattggtaac caatttattt taaaagcccg tcaatttaat ttctggtgqt gcaqaagtta
                                                                     120
gaaggtaaag cttgagaaga tgagggtgtt tacgtagacc aqaaccaatt taqaaqaata
                                                                     180
cttgaagcta gaaggggaag ttggttaaaa atcacatcaa aaaqctacta aaaqqactqq
                                                                     240
tgtaatttaa aaaaaactaa ggcagaaggc ttttggaaga gttagaagaa tttggaagg
                                                                     299
      <210> 519
      <211> 464
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(464)
      <223> n = A, T, C \text{ or } G
      <400> 519
gctgcacatc ggaggaaaac tcggtaaagc agaatgaggt tgatatgttg aatgtatttg
                                                                      60
attttgaaaa ggctgggaat tcagaaccaa atgaattaaa aaatgaaagt gaagtaacaa
                                                                     120
ttcagcagga acgtcaacaa taccaaaagg ctttggatat gttattgtcg gcaccaaagg
                                                                     180
atgagaacga gatattccct tcaccaactg aatttttcat gcctatttat aaatcaaagc
                                                                     240
attcagaagg ggttataatt caacaggtga atgatgaaac aaatcttgaa acttcaactt
                                                                     300
tggatgaaaa tcatccaggt atttcataca gtttaacaga tcgggaaact tctgtgaatg
                                                                     360
tcattgaagg tgatagtgac cctgaaaagg ttgagatttc aaatggatta tgtggtctta.
                                                                     420
acacatcacc ctcccaatct gttcagttct ccagngtcaa aggc
                                                                     464
      <210> 520
      <211> 221
      <212> DNA
      <213> Homo sapien
     <400> 520
60
acatgcccca cattagatct ctagactcat tcatcctaca tacctacttt gtatcctttg
                                                                     120
acctacatet coctacttee tectecagte eccacecee acceaetggt getaaceaet
                                                                     180
gtttcattcc ctttttcatt ctacatatgt gagatcatgc t
                                                                     221
     <210> 521
     <211> 312
     <212> DNA
     <213> Homo sapien
     <220>
     <221> misc feature
     <222> (1)...(312)
     <223> n = A,T,C or G
     <400> 521
ctgatagett tetettegee tagattaata tettetnnet teccatteae ageceecace
                                                                     60
gacatcaaag ctttgctgtt ttatctgtca aaaatgtctt cacacttttc attcttaaat
                                                                    120
aaaagtgctg agtaaggaca ttttcacaac aaatttttat tttacaaaac ttacaatgat
                                                                    180
ttgaatccaa aacaactttc attatttaac tgtaaaqtaa atatatatt tattaqqqqt
                                                                    240
```

```
gtottagttc attttgtgct gctttaacag tgtatccttg tgatagttgt ggggtggggg
                                                                        300
                                                                        312
aggggggaag ga
     <210> 522
      <211> 336
      <212> DNA
      <213> Homo sapien
      <400> 522
ccttctttcc ccactcaatt cttcctgccc tgttattaat taagatatct tcagcttgta
                                                                         60
gtcagaccca atcagaatca cagaaaaatc ctgcctaagg caaagaaata taagacaaga
                                                                        120
ctatgatatc aatgaatgtg ggttaagtaa tagatttcca gctaaattgg tctaaaaaaag
                                                                        180
aatattaagt gtggacagac ctatttcaaa ggagcttaat tgatctcact tgttttagtt
                                                                        240
ctgatccagg gagatcaccc ctctaattat ttctgaactt ggttaataaa agtttataag
                                                                        300
atttttatga agcagccact gtatgatatt tttaag
                                                                        336
      <210> 523
      <211> 172
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(172)
      <223> n = A, T, C or G
      <400> 523
ngacnggene ntggetatgt ntatagatag ggetttaace actatetgng aageangagn
                                                                        60
                                                                        120
gacannatte ttgeteteae atnecaengg anacgtattt etettetet aenagegaag
aaccatctnt ttctaaagcc cccattctat tgcccttgct tttctctggc tt
                                                                        172
      <210> 524
      <211> 471
      <212> DNA
      <213> Homo sapien
      <400> 524 -
ccagacctgc agaaaaactt agcacagctc aatctgctgt tttgatggct acagggttta
                                                                        60
tttggtcaag atactcactt gtaactattc caaaaaaattg gagtctgttt gctgttaatt
                                                                        120
tctttgtggg ggcagcagga gcctctcagc tttttcgtat ttggagatat aaccaagaac
                                                                        180
taaaagctaa agcacacaaa taaaagagtt cctgatcacc tgaacaatct agatgtggac
                                                                        240
aaaaccattg ggacctagtt tattatttgg ttattgataa agcaaagcta actgtgtgtt
                                                                        300
tagaaggcac tgtaactggt agctagttct tgattcaata agaaaaatgc agcaaacttt
                                                                        360
taataacagt ctctctacat gacttaagga acttatctat ggatattagt aacatttttc
                                                                       420
                                                                        471
taccatttgt ccgtaataaa ccatacttgc tcaaaaaaaa aaaaaacctt c
      <210> 525
      <211> 332
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(332)
      <223> n = A, T, C \text{ or } G
```

```
<400> 525
ccccnctgta ttccagcctg ggtgacccca tctcanggaa gaaaagttac cagatgtcgn
                                                                      60
gggtaaaggt tggtcttcaa gtggcctcat aagttgtctt gcatttaaat tcagggaatt
                                                                     120
cattggacca ataggttaca ttttcgttcc ttttttgttt tggttcatct gttaagcagt
                                                                     180
gggggcctaa ttactgctcc tttgtaaaaa cacattttcc caaagaacac tgaattaccg
                                                                     240
ttcaaactgg ttgttgatgg gtaataaggg ctgtttttgc tgccccaaaa gggcttaaca
                                                                     300
atttaggcgg atagtttact taaaaaaaaa aa
                                                                     332
      <210> 526
      <211> 440
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(440)
      <223> n = A, T, C \text{ or } G
      <400> 526
ccaggttacc tcccctaaca gatgtggtgt tctgangggt tggttaagtg cccgaggaaa
                                                                     60
ataggeetta actgttaaca tetacagaga agaaageatg gteacactgg caaggagtaa
                                                                    120
gaagggattg ggtaaaagaa aatgggagag aaaagggaaa aaagttttgg caagacaatt
                                                                    180
240
nctgtctctc tgatcagngg aaaagtgaaa atttctagta tctagcacta acgtatgacc
                                                                    300
caactttgag ggatcacaag ctagaacaag ttgaggattt aaaatcctgg ataattatat
                                                                    360
acttaaagtt catgagcata aagctcactt gaccatgcag aaatgctggg aagcagggtg
                                                                    420
catggcatgg gaatacatct
                                                                    440
     <210> 527
     <211> 124
     <212> DNA
     <213> Homo sapien
     <220>
     <221> misc feature
     <222> (1)...(124)
     <223> n = A,T,C or G
     <400> 527
tttccatatg tctgttgggt gcataaatgn cttcttctga gaagtgtctg ttcctatcct
                                                                     60
ttgccccctt tttgaggact taaatgttag acctaagacc ataaaaaccc tagaagaaaa
                                                                    120
ccta
                                                                    124
     <210> 528
     <211> 162
     <212> DNA
     <213> Homo sapien
     <220>
     <221> misc_feature
     <222> (1)...(162)
     <223> n = A, T, C or G
     <400> 528
```

```
ctgcgggaga aatatgggga caagatgttg cgcangcaga aaggtgaccc acaagtctat
                                                                         60
gaagaacttt tcagttactc ctgccccaag ttcctgtcgc ctgtagtgcc caactatgat
                                                                        120
aatgtgcacc ccaactacca caaagagccc ttcctgcagc ag
                                                                        162
      <210> 529
      <211> 409
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(409)
      <223> n = A, T, C \text{ or } G
      <400> 529
cctttaaaat atagcttata aaatgtatac tatnngccag gagagctcac atttttctgc
                                                                         60
agttttccag tggacctgcc tatggaatac tgtaaagaaa aatctgcaaa aatattccta
                                                                        120
                                                                        180
gcaattgaat cagtgctttt aaataaaaga agtggagagg ggcttggtta aattattctg
acaagttttc ttgctagtgg ttgccaaaat taaggatatt tgaagtgtcc tatcacccaa
                                                                        240
atttggcttt aagaaaaagc tatattctgn gtctataggg tgaagcccac actatctgtg
                                                                        300
ctgcattctc aatgatacaa tacctatctg gaaactttcc tgttttgcca atgggtgcac
                                                                        360
aaatctaaaa cattttatca caaaaggtac ttgaatttaa atttctttt
                                                                        409
      <210> 530
      <211> 325
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(325)
      <223> n = A,T,C or G
      <400> 530
                                                                         60
ccgccagtgt gatggatatc tgcagaattc gccctttcna gatttgngcc cgggcaggtc
catggctagg attatagata gttgggtggt tggggnaaat gagtgaggca ggagtccgag
                                                                        120
                                                                        180
gaggttagtt gtggcaataa aaatgattaa ggatactagt ataagagatc aggttcgtcc
                                                                        240
tttagtgttg tgtatggcta tcatttgttt tgaggttagt ttgattagtc attgttgggt
                                                                        300
ggtaattagt cggntgttga tganatattt ggaggtgggg atcaatagag ggggaaatag
                                                                        325
aatgatcagt actgcggcgg gtagg
      <210> 531
      <211> 173
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(173)
      <223> n = A, T, C \text{ or } G
      <400> 531
                                                                         60
ccaattgatt tgatggtaag ggagggatcg ttgaccncgt ctgttatgta aaggatgcgt
agggatggga gggcgatgag gactaggatg atggcgggca ggatagttca gacggtttct
                                                                        120
atttcctgag cgtctgagat gttagtatta gttagttttg ttgtgagtgt tag
                                                                        173
```

```
<210> 532
       <211> 395
       <212> DNA
       <213> Homo sapien
      <220>
       <221> misc_feature
      <222> (1)...(395)
      <223> n = A, T, C \text{ or } G
      <400> 532
caggicctac tatgggigtt aaattittia cictototac ngggittitt cotagigtoo
                                                                          60
aaagagetgt teetetttgg actaacagtt aaatttacaa ggggatttag agggttetgt
                                                                         120
gggcaaattt aaagttgaac taagattcta tcttggacaa ccagctatca ccaggctcgg
                                                                         180
taggtttgtc gcctctacct ataaatcttc ccactatttt gctacataga cgggtgtgct
                                                                         240
ettttagetg ttettaggta getegtetgg tttegggggt ettagetttg geteteettg
                                                                         300
caaagttatt tctagttaat tcattatgca naaggtatag gggntagtcc ttgctatatt
                                                                         360
atgcttggnt ataatttttc atctttccct tgcgg
                                                                         395
      <210> 533
      <211> 290
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(290)
      <223> n = A, T, C \text{ or } G
      <400> 533
ctgaaccatt atgggataaa ctggtgcaaa ttctttgcct tctctacttc tcactgattg
                                                                          60
aacataagct tccagggctc ccctgaaaac caaaatgaaa acaatgtcaa aatattagat
                                                                         120
aaatcacata aaacagttaa ggggatacca atatataaaa attattaggt aagctcattt
                                                                         180
ctggaactgt taatgctcgg tttcacaatc caagnngacc aacagccttc actcagntac
                                                                         240
tggnagtgnt actatggtta ctacngntac tacctttagt gtnaaaaact
                                                                         290
      <210> 534
      <211> 334
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(334)
      <223> n = A, T, C \text{ or } G
      <400> 534
ccgccagtgt gatggatatc tgcagaattc gcccttagcg agnnagccgg gcaggtccat
                                                                          60
ggctaggttt atagatagtt gggtggttgg tggggnatga gtgaggcagg agtccgagga
                                                                        120
ggttantttg tggcaataaa aatgattaag gatactagta taagagatca ggttcgtcct
                                                                        180
ttagtgttgc gtatggctat catttgtttt gagggtagnt tgattagnca ttgttgggng
                                                                        240
gtaattantc ggctgttgat ganatatttg gaggtgggga tcaatanagg gggaaatana
                                                                        300
atgatcagtn ctgcggcngg tnngacctcn gccc
                                                                        334
```

```
<210> 535
      <211> 557
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(557)
      <223> n = A, T, C \text{ or } G
      <400> 535
nccataagct tcagtgcgca aaaggtcaag gccagtgtta atttgttatt tcttaaataa
                                                                       60
ctttcccttt catttttaaa ttataaattt aacttctaac atgttttatg gttaaaattg
                                                                      120
                                                                      180
tacttttttc ctttagcgac attcaaatgc atcacaatca ctttgtgaaa ttgttcgcct
gagcagagac cagatgttac aaattcagaa cagtacagag cccgaccccc tgcttgccac
                                                                      240
tctagaaaag tatgtgtaaa actctgttct tgttcttctt tcatattgat gctgttccat
                                                                      300
gtgttaccat tgtgagtggt tggtaagtgt tccttatgtg ggaatcatgt gccttgaaaa
                                                                      360
                                                                      420
taaccttggg tgggtgagaa ggtagggaaa cctgcttctt ttatctcaag taaaagtttt
ggcagggtaa agaagataaa tgacatttat atctagactt ttgagttttc caattatttg
                                                                      480
                                                                      540
gtaaaaatgg gaaattctgt agaagccctt ccttaaaaaat gggggaagtc catttnanaa
aattaactgg taggtca
                                                                      557
      <210> 536
      <211> 372
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(372)
      <223> n = A, T, C \text{ or } G
      <400> 536
gttccaacct tcatttctga aactgttcta gagcacngtg tctttctcgt agttcataac
                                                                       60
ttaccccttc agtctagaat tagaattaca ttatctgttt tactacttta ctagactgta
                                                                      120
                                                                      180
agctcctaga agataaggac tagggagttc atctctgtat tccaccagaa ggtacagtga
                                                                      240
ctcatatcta gagtctttag atgaaactta ctgagttgaa taacttaata tatttctgtt
                                                                      300
ttcattccca agggaggcca tgtctggaga tagaccttga atttaataaa ttttaggcac
360
                                                                      372
ggaagtcact gg
      <210> 537
      <211> 284
      <212> DNA
      <213> Homo sapien
     <220>
     <221> misc_feature
     <222> (1)...(284)
     \langle 223 \rangle n = A,T,C or G
     <400> 537
ccttctgatg caaacagaaa ggaaatgttg tttggangcc ttgctagacc tggacatcct
                                                                       60
atgggaaaat ttttttgggg aaatgctgag acgctcaagc atgagccaag aaagaataat
                                                                      120
attgatacac atgctagatt gagagaattc tggatgcgtt actactcttc tcattacatg
                                                                      180
```

177

240 actttagtgg ttcaatccaa agaaacactg gatactttgg aaaagtgggt gactgaaatc ttctctcaga taccaaacaa tqqqttaccc agaccaaact ttgg 284 <210> 538 <211> 293 <212> DNA <213> Homo sapien <400> 538 gtacatagta ggtgtatata tttatgggct atataagatg ttttgataca ggcatgtaat 60 gtgaaacaag cacatcaaca agaatggggt atccatcccc taaaacattt gtcctttggg 120 ctacatgica titcctaatg taaaqaaaat ggacaqacag aaccaacatt gatttgactg 180 ggtgaaaaag tccatttgag ttgggagcag gggttgtgtt cctggatttg ggttgttagg 240 acagtgtaaa aaggcttcac aggggaacat tcttttctga taaaggaaag cag 293 <210> 539 <211> 468 <212> DNA <213> Homo sapien <220> <221> misc_feature <222> (1)...(468) $\langle 223 \rangle$ n = A,T,C or G <400> 539 tttcnataaa ctttattttt agagcagttt taagnnggta gcaaaattga ttagaaggna 60 cagagatgtc ccatacacct cctactccca cacatgcaca gccttcccca ttatcaatag 120 cccccaacag agggatacat ttgttaacaa ctgacgaacc tacatatcat tatcacccaa 180 agtccacagt ttatattatt ccttctggag aattttcaaa tacaqaaatt cctctaccaq 240 gaataaacta ncaatttcct ctcggctttc tataaattta attattattt caqaaattaq 300 cctatcttta caggagaaaa tgttataaac catgaaaaga ctatcaaata cacaaggaag 360 tgaatgntat ataaaaaatg taccatctcc taaacaacta cctgcattcc cttcttqttq 420 gtaagttata atttgnnata gttctgatca tctgtttaat taatttgc 468 <210> 540 <211> 397 <212> DNA <213> Homo sapien <220> <221> misc_feature <222> (1)...(397) <223> n = A,T,C or G <400> 540 ctgttttatt aattccccca tttgcagcac acttntctct tccaacattc atcagtcaga 60 tcagagtcca cggtcttttc aaaatttaga taaactggct tacattttgt aatgatgtcc 120 ccagacaaca ccccactcca acccattctg tttgttacta ttagtttaca acatgcatgt 180 gcctttactt tcattttcat agtatttaaa aatggaaggg cactcccaaa tttactttaa 240 cccctttaat aatctctctc ctcctgctct ctctggtcct ccagacaact gttgatttac 300

tttcctttat gatggattag tttgcatttt ctagaatttt atatgactga catataaagn

360

397

<210> 541

ttttatgttt ctcccctttg ggtttcttca tgtggca

```
<211> 248
      <212> DNA
      <213> Homo sapien
      <400> 541
cctagatagg ggattgtgcg gtgtgtgatg ctagggtaga atccgagtat gttggagaaa
                                                                         60
taaaatgtgc atagtggggg ttttatttta agtttgttgg ttaggtagtt gaggtctagg
                                                                        120
gctgttagaa gtcctaggaa agtgacagcg agggctgtga gttttaggtg gagggggatt
                                                                        180
gttgtttgga agggggatgc gggggaaatg ttgttagcaa tgagaaatcc tgcgaatagg
                                                                        240
                                                                        248
cttccgqc
      <210> 542
      <211> 366
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (366)
      <223> n = A, T, C or G
      <400> 542
aatcggccct ctagatgcat gctcgagcgg ccgccagtgt gatggatatc tgcagaattc
                                                                        60
gcccttgagc gatancgcgg gcaggtccaa ttgatttgat ggtaagggag ggatcgttga
                                                                        120
conceptctet tatetaaage atecetagee ategegagee gategageact ageateatee
                                                                        180
cgggcaggat agttcagacg gtttctattt cctgagcgtc tgagatgtta gtattagtta
                                                                        240
                                                                        300
qttttgttgt gagtgttagg aaaagggcat acaggactag gaagcagata aggaaaatga
ctatgagggc gtgatcatga aaggtgataa gctcttctat gataggggaa gtagcgtctt
                                                                        360
                                                                        366
gtanac
      <210> 543
      <211> 460
      <212> DNA
      <213> Homo sapien
      <400> 543
                                                                        60
cctactatgg gtgttaaatt ttttactctc tctacaaggt tttttcctag tgtccaaaga
gctgttcctc tttggactaa cagttaaatt tacaagggga tttagagggt tctgtgggca
                                                                        120
aatttaaagt tgaactaaga ttctatcttg ggcaaccagc tatcaccagg ctcggtaggt
                                                                        180
ttgtcgcctc tacctataaa tcttcccact attttgctac atagacgggt gtgctctttt
                                                                        240
agetgttett aggtageteg tetggttteg ggggtettag etttggetet eettgeaaag
                                                                        300
ttatttctag ttaattcatt atgcagaagg tataggggtt agtccttgct atattatgct
                                                                        360
                                                                        420
tggttataat ttttcatctt tcccttgcgg tactatatct attgcgccag gtttcaattt
                                                                        460
ctatcgccta tactttattt gggtaaatgg tttggctaag
      <210> 544
      <211> 116
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(116)
      <223> n = A, T, C or G
```

```
<400> 544
ccgccagtgt gatggatatc tgcagaattc gccctttgga gngctngcgc ccgggcaggt
                                                                        60
ctgtttcagc agetectect tettettece gegangatet egageettga tettgg
                                                                       116
      <210> 545
      <211> 380
      <212> DNA
      <213> Homo sapien
      <220>
     <221> misc feature
      <222> (1)...(380)
      <223> n = A,T,C or G
      <400> 545
cgacggatcg atnagctnga tatcgaattc ggacgagcat ggcgtattgc tgcagatatg
                                                                        60
gattetteag aatgeteeat gacaaatgta etgaegggaa gnenatetaa aggaggeatt
                                                                       120
gtnatgagag aaaggtctcg agctccagat aaagagagat acagagttct tggaattgga
                                                                       180
gttgcagaaa cagtaagaca atcgattgtg gggaagcgtt cttttagaga atctttggcc
                                                                       240
ttcactccaa agcgttgttc ttcatcaata ataagtagct cgtgccgaat tcctgcagcc
                                                                       300
cgggggatcc actagttcta gagcggccgc caccgcggag gagctccagc ttttgttccc
                                                                       360
tttagtgagg gttaatttcg
                                                                       380
      <210> 546
      <211> 418
      <212> DNA
      <213> Homo sapien
      <400> 546
ccagggcaat taggcaggag aaggaaataa agggtattca attaggaaaa gaggaagtca
                                                                        60
aattgtccct gtttgcggat gacatgattg tatatctaga aaaccccatt gtctcagccc
                                                                       120
aaaatctcct taagctgata agcaacttca gcaaagtttc aggatacaaa atcaatgtac
                                                                       180
aaaaatcaca agcattctta tacaccaata acagaccaac agagagccaa attatgagtg
                                                                       240
aactcccatt cacaattgct tcagagaata aaatacctgg gaatccaact tacaaqqqat
                                                                       300
gtgaaggacc tcttcaagga gaactacaaa ccactgctca aggaaataaa agaggataca
                                                                       360
aacaaatgga agaacattcc atgctcatgg gtaggaagaa tcaatatcat gaaaatgg
                                                                       418
      <210> 547
      <211> 172
      <212> DNA
      <213> Homo sapien
      <400> 547
cctgaggttg ggagaaattt tgtccatttc tttagaacca aaattggcaa ccagagagta
                                                                        60
tttggatgtt acacaaaata tctagtttcc ctttctagcc taaattgggt tgtttatagc
                                                                       120
accegtetet ceattigaga aaaatggtta ggatgetggt geagggatga gg
                                                                       172
      <210> 548
      <211> 367
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(367)
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180

<223> n = A, T, C or G

```
<400> 548
ggtctgactt aagagaaaca atggaaggca agaggcagta gaataatata ttcaaaagat
                                                                        60
qcaaaqqaaa aaaacctctc aqccacqaat tccttatcca qcaattattt ttcaaaaaatq
                                                                       120
aaaataacac aaagacttag ccagataaac agaaacatta actgaagttg ttgctggcag
                                                                       180
acctaccata taaaaataaa aaactctaaa aaaattccta tggctaaaag caagttacag
                                                                       240
aagacagtca cttgaatcca cattttaaaa aaagcactga tatacgtaat attgacatta
                                                                       300
taaaaqacag taaaaatgca tttcttcttt ataataaatn gcttattaaa taacatgtgt
                                                                       360
                                                                       367
ataatqq
      <210> 549
      <211> 418
      <212> DNA
      <213> Homo sapien
      <400> 549
                                                                        60
ccaaatcaga acctagagtg agcattctat aaactcacct ttgctttgat ccttgaagat
cacaagtttt gatactgttg aaatctctac tctttcaaca ctttaattaa atggcattta
                                                                       120
gaatttcata tacttctgtt gttgtttcca caatcttaaa ctggatttag aaatacttat
                                                                       180
aatgtaaatg caagagettt aacttagtaa cegtatttee tattttttgt tgtttttett
                                                                       240
ttgccagaat ttctgtttgt ctacaataaa gtccagcgaa atacagtatt tggttaggtt
                                                                       300
acttgttaac ataaaatttt atcatttgta gagtttttac ttaaccttcc tattctctag
                                                                       360
tototataat ottotaatga agataaccag ttacgaatat otootatacc atattagg
                                                                       418
      <210> 550
      <211> 234
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(234)
      <223> n = A,T,C or G
      <400> 550
                                                                        60
cctacccgcc gcagnactga tcattctatt tccccctcta ttgatcccca cctccaaata
tctcatcaac aaccgactaa ttaccaccca acactcacaa caaaactaac taatactaac
                                                                       120
atctcagacg ctcaggaaat agaaaccgtc tgaactatcc tgcccgccat catcctagtc
                                                                       180
                                                                       234
ctcatcgccc tcccatccct acgcatcctt tacataacag acgaggtcaa cgat
      <210> 551
      <211> 542
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(542)
      <223> n = A, T, C or G
      <400> 551
cacccctacc conntectca taaaagttnc tetecetgga teetettttt ceeteatgag
                                                                        60
tgcccggttg cccaagtcaa aaacctggga gtgatataaa ctccccacac atccagtcag
                                                                       120
```

tcactcatca actctattga ttctgtctgc taaatatatn tcaattgtat taacttaaac

```
atatgcatan ggcactttct tetteactge atttttgtgg getgeactta cettteaggt
                                                                        240
aacgacaaca ctggcccctc ttgcccttct agtcagaagt gccaaaatga tgagagctag
                                                                        300
ccatgacaaa cccacagcca acattacact gaatgtgcaa aactggaagg gcatccaaac
                                                                        360
agaggaggg agagaggaat agacaggaag tcaaactgtc tctgtttaca gatgacatgt
                                                                        420
ttctatatct ataaagcccc atagtcttgg ccccaaagct tcttctgctg ataaacttta
                                                                        480
gcaaagtctt agcatacaaa atcaatgtgc aaaaattact aacagtccta tacatcaagt
                                                                        540
                                                                        542
      <210> 552
      <211> 411
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature .
      <222> (1) ... (411)
      <223> n = A, T, C or G
      <400> 552
cctggntgac aaggaggtgc ctgtnatgtg aagatttgag gaaagagcat tccaggcagg
                                                                         60
gggaaggctt gatgcaaagg gtctactgca ggcattagct gagcttattt aaagatcaga
                                                                        120
atgaaggcca ttgtggctag aacagagtgg acaggaagga atggtaccag gcaaagctga
                                                                        180
agaagttggc aggattgagc tctcataant catqqcaaaq aqttcccatt tcattqtttq
                                                                        240
acggaaataa attggaaggt cttaagtagg agaagatttg attagattta cattttacqa
                                                                        300
agaagcactc tggatgttat gtgaagaaat ggcctttgca gggcaagggt ggaaacaaag
                                                                        360
agatcagtta ggaaattatt ggagtagctg aggattggat gaggggatgt g
                                                                        411
      <210> 553
      <211> 631
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(631)
      <223> n = A, T, C \text{ or } G
      <400> 553
ccgggattag aactaaaaca agtgagatca cccctctaat tatttctgaa cttggttaat
                                                                        60
aaaagtttat aagattttta tgaagcagcc actgtatgat attttaagca aatatgttat
                                                                       120
ttaaaaatatt gatccttccc ttggaccacc ttcatgttag ttgggtatta taaataagag
                                                                       180
atacaaccat gaatatatta tgtttataca aaatcaatct gaacacaatt cataaagatt
                                                                       240
totottttat acottoctoa otggococot coacotgoco atagtoacoa aattotqttt
                                                                       300
taaatcaatg acctaagatc aacaatgaag tattttataa atgtatttat gctgctagac
                                                                       360
tgtgggtcaa atgtttccat tttcaaatta tttanaattc ttatgagttt aaaatttgta
                                                                       420
aatttetaaa teeaateatg taaaatgaaa etgttgetee attggagtag teteecacet
                                                                       480
aaatatcaag atggctatat gctaaaaaga gaaaatatqq tcaagtctaa aatgqctaat
                                                                       540
tgtcctatga tgctattatc atagactaac gacntttatc ttcaaaacac caaattgtct
                                                                       600
ttagaaaaat taatgtgatt acaggtagag g
                                                                       631
     <210> 554
     <211> 558
      <212> DNA
      <213> Homo sapien
```

```
<220>
      <221> misc feature
      <222> (1)...(558)
      <223> n = A, T, C \text{ or } G
      <400> 554
ccaggntagt ctccaactcc tgaccttagc tgatccaccc acctcggcct cccaaagtgc
                                                                         60
tgggattaca ggcatgagcc actgcgcccg gccaaacttg atatgcattt ttaaataagt
                                                                        120
taatacatta ttcatggttt agtctcatta tatattctat ggtccacttt gaaatttcat
                                                                        180
                                                                        240
ctaaccaaaa tcatcttcat cctgcaattt gaggtttgga cacaatgggg attgatcagt
aatttcttca tatgcccttt ctcaaggaaa tagtttccta tgaaaaaaaa gtcctatgtt
                                                                        300
ttcatgtaag ttctcttttt ggagaagaaa aggagacatt cttacttagc actctcagtt
                                                                        360
ttacaaaacg ctgccaacct taaaatttgt ctattgattc ccaaggcaca caaccaatag
                                                                        420
                                                                        480
totgtcaata accoggaata acatttottt aaggooccag taactttcac atgtttgggt
                                                                        540
tccaatcctc acctagaatc ttgttaagaa aagtaaacca ttcactcctc tagaaactct
                                                                        558
aaggttgctt cttagggg
      <210> 555
      <211> 212
      <212> DNA
      <213> Homo sapien
      <400> 555
                                                                         60
ccaggtattt gcataatggc ttttcttctg ttgcctttgt tcctttgtgg ccccagctaa
                                                                        120
ttgcctgaga gtgccactgt tagttttcaa ctctttctga tagaaaccct gtgtactaac
                                                                        180
atggaaatct taggtaatct gctttttcaa agcacaatgc agaatttatt ggcggtggtg
taactttaag aatatccgag aagccaccaa gg
                                                                        212
      <210> 556
      <211> 219
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(219)
      <223> n = A, T, C \text{ or } G
      <400> 556
                                                                         60
ccatgtgtct atctggagag aaggggaaac agcaagtgca aaggccctga gatggaacat
                                                                        120
atctggagaa ttcgaagaat ggtaagaagg ccagagtgga gcagaacaag tgtgggagag
agttgtagga gatgagatca aaggctagga atgaagtgta aggccatgtc atgtgacctt
                                                                        180
                                                                        219
gtatgtcctt gtaaggcttt ttttttttt tttnancct
      <210> 557
      <211> 482
      <212> DNA
      <213> Homo sapien
      <400> 557
                                                                         60
cctactatgg gtgttaaatt ttttactctc tctacaaggt tttttcctag tgtccaaaga
gctgttcctc tttggactaa cagttaaatt tacaagggga tttagagggt tctgtgggca
                                                                        120
aatttaaagt tgaactaaga ttctatcttg gacaaccagc tatcaccagg ctcggtaggt
                                                                        180
                                                                        240
ttgtcgcctc tacctataaa tcttcccact attttgctac atagacgggt gtgctctttt
```

agetgttett aggtageteg tetggttteg ggggtettag etttggetet cettgeaaag

```
ttatttctag ttaattcatt atgcagaagg tataggggtt agtccttgct atattatgct
                                                                        360
tggttataat ttttcatctt tcccttgcgg tactatatct attgcgccaq qtttcaattt
                                                                        420
ccatcgccta tactttattt gggtaaatgg tttggctaag qttqtctqqt aqtaaqqtqq
                                                                        480
ag
                                                                        482
      <210> 558
      <211> 679
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(679)
      <223> n = A,T,C \text{ or }G
      <400> 558
ctgtnaaaat tctgaaccta tccccaaaag aaaaaccgtg aaatacaagt tttaggaggt
                                                                         60
ggagcaaaga aaagccaagt tatttaaaac caataaacac aagagacaat tctgctggag
                                                                        120
aatttacttt ctccaaaaca tcaaatggac tttaaagcag aagaccacat tttatqaqaa
                                                                        180
agttatgtca ctgaaaagct tcatgtaaag tgactttgta aatggaatat ttttaaatga
                                                                        240
taaaaagaaa ataacttttc caggaatcct ttggagaggc tgataaccag atattaaatt
                                                                        300
atcaattttg ccaaagtgga cttttaaaaaa atgtgttact tttaaaaaact aacttgaaag
                                                                       . 360
aatttatgag gcaatctatc tgagtatgtt tattgttgct ccattggctt tcaggatttt
                                                                        420
ggtcatttca ctgttaactc ttacatcaga gaataaagaa aagaaaatga aactttgtta
                                                                        480
ggaactggga tggaaaatgt agtcccagac agatctactg acctcgactg agtttcaqaa
                                                                        540
atatcccagg attitggtta ttcatgcctt tcttttgtga ctttctttca aattaqccaa
                                                                        600
ttaaagatac cccttcaatc accggtgaca tcagtacaac agtttttcaa cagttttctc
                                                                        660
tctcctgacc aaacagttt
                                                                        679
      <210> 559
      <211> 488
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(488)
      <223> n = A, T, C \text{ or } G
      <400> 559
ccccactgta ctccagcctg ggtgacccca tctcaaagaa gaaaagttac cagatgtcat
                                                                         60
gggtaaaggt tggtcttcaa gtggcctcat aagttgtctt gcatttaaat tcagggaatt
                                                                        120
cattggacca ataggttaca ttttcgttcc ttttttgttt tggttcatct qttaaqcaqt
                                                                        180
gggggcctaa ttactgctcc tttgtaaaaa cacattttcc caaagaacac tqaattaccq
                                                                        240
ttcaaactgg ttgttgatgg gtaacaaggg ctgtttttgc tqccccaaaa qqqcttaaca
                                                                        300
atttaggcgg atagtttact taaaaaaaaa aatcctttgg agacatactg aaaatgcaaa
                                                                        360
ctagtttcta aattatcaat tccctacatg aanaagcagt ttgccanagt ttagtctcan
                                                                        420
aaaatgactg gttggctcta tttaaatcan aacccaattt ctacgcacct gcccgcccgq
                                                                        480
ccaagggc
                                                                        488
      <210> 560
      <211> 602
      <212> DNA
      <213> Homo sapien
```

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<220> <221> misc_feature <222> (1)...(602) <223> n = A, T, C or G<400> 560 60 cctanttaag aattccttgc cttagtggtg aacaaggact aaacacagac aatgggtgaa acacagacgc taattcacat aacagagagt aggcaacctt aagaatgaat tgatgcagac 120 tcctatagaa ttcctctgtt atgactgggt tcttattttc tcctccttgt atgtagttga 180 aatttcatca ttatgaatag ttccttggat cttttttaa agttgtgaat gcgagtgttt 240 300 ggctttgtaa tacaactttt tagtatccag aagataacca gtgctctacc aataaagatc ttttgataca aagggtttta acttctgcca gttcttactc attttttca ggttttttat 360 acatttctta aacaacacat acattatgta aaatataaga attaatgtac attctcaagg 420 480 ccagattcag tgacaaaatg cactacccga atctagtaac acatttactc cttgctgcat ataagtggcg tgtaagaaat acagggtata ttgttttgtg atccatgcag taaatgttca 540 600 caaatatcag gcaaacaact agacgntctt cagctactaa aattaactgt cccagtcaca 602 aa <210> 561 <211> 683 <212> DNA <213> Homo sapien <400> 561 60 gtctattttt aaaaagaaag aaaaaaacca cttttttata gtccctagct ttgccatatg 120 cccgccttaa gtggaaggaa agttaatcac ttaactatgt tttataaaaa gaaaaaaggg cttqqaatqc tattactqtt cacacaaaqt atgattctgt ttgaataagg caaatgctcc 180 tttttttaaa aaaagacatt actgtaatat caaaaaccgt ggcagtttgt atacaactct 240 qqqcttqatt ttttttaaaa aaacagaatg aattgatgtc ttattttata aatgttctat 300 atttattagg agaaaacttt atattgcctt ttttatcaat catgtaacag gcttatagct 360 ttccaacaga gctgcttgcc aaacaatttt ttttgtttat taaacagtgc tgaaacaaac 420 480 aggatcagca tttacttaag atgttaagaa tgaggacttt taatcagccg aaccaagata ttgttacctg tatgcattcc caaagtctag atgctcagta tgttcagtca tatctttcag 540 aatcagtgaa ccgattaccc tttttttggt attcactcta catctgccaa cctagttcac 600 cttggttttg tgtctgctgt agaagggaac cataacttgg ttaaaccgta gggattatca 660 683 ttgtatacat gctgtgaaca tgt <210> 562 <211> 420 <212> DNA <213> Homo sapien <400> 562 60 gcactttttt tccagtaagg attcatctct tgctctccta tatggtcatt atattttata ttttacatat ttataaacat gacatatgta tttatgttcc acaaagggct ttgaatagaa 120 tttacacata gagttccctg ggttgatgtg tttatcaaaa tggaagataa agtgaattaa 180 ttacttaaat atttaacact attgaataga aataatttcc ccaatattgc ttcatgattt 240 300 agacagteta ttaaatgttt aagcaaggca ctagactaag tttattaaga caaattttgg aatatgtgca gaaatatgac ctggctaata gtacagagtc aaagctggtt gaatggtgtt 360 atatagtgga ttcagattga tgtggcagtg gtggttacac taggggcact aaggttatcc 420

<210> 563

<211> 482

<212> DNA

<213> Homo sapien

```
<400> 563
ctccacctta ctaccagaca accttagcca aaccatttac ccaaataaag tataggcgat
                                                                         60
agaaattgaa acctggcgca atagatatag taccgcaagg gaaagatgaa aaattataac
                                                                        120
caagcataat atagcaagga ctaaccccta taccttctgc ataatgaatt aactagaaat
                                                                        180
aactttgcaa ggagagccaa agctaagacc cccgaaacca gacgagctac ctaagaacag
                                                                        240
ctaaaagagc acacccgtct atgtagcaaa atagtgggaa gatttatagg tagaggcgac
                                                                        300
aaacctaccg ggcctggtga tagctggttg tccaagatag aatcttagtt caactttaac
                                                                        360
tttgcccaca gaaccctcta aatccccttg taaatttaac tgttagtcca aagaggaaca
                                                                        420
gctctttgga cactaggaaa aaaccttgta gagagagtaa aaaatttaac acccatagta
                                                                        480
gg
                                                                        482
      <210> 564
      <211> 302
      <212> DNA
      <213> Homo sapien
      <400> 564
ctggaagtga aggtactaat atacaaatgg ctcttgtttc tgaatatgtg atataatttg
                                                                        60
tgaatctttg gaaactgaat tttttctatg gagtgcaaat atagaagggt tattttacaa
                                                                       120
tgtttgttgt gaaaagaatt cactttgtaa acaactatta aggctggaag tttagtgaag
                                                                       180
gtgcatagtt ttgaaagcta cacaggtgaa aaatcaaact tattgtttgt aattttgctg
                                                                       240
ttacatgtta agttactttg acagcaattt tctaatgata atgtgattta tgatttaaaa
                                                                       300
gg
                                                                       302
      <210> 565
      <211> 554
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(554)
      <223> n = A.T.C or G
      <400> 565
ccanngtgac atcatggcaa tacagcaaga attctgnnat ttatttagaa gcctcaagga
                                                                        60
gaaggateet ggageeeetg aatgagagtt tetteteeat geeteteeee agteaaaata
                                                                       120
catggaaata ttcatagaag cattgtaccc agcatgataa ggaaggatgg agaatggttc
                                                                       180
cttatatctc tgttcacaag acatcaacac tcttaagtaa ctgtatgaaa taaattctct
                                                                       240
gctgaaagca aataaaccat ctgaaaggtc ttctggttac ttacacagat ttcctagaga
                                                                       300
atctgaaatc agcctaacag ggaagattaa tttttaaatg aatccaagtt aatgaaagca
                                                                       360
aagaactctt atacagaaat acattttcct attataaagc aggactacct tccctaattt
                                                                       420
ctgatagacc taggacaatt tgaatgggca ttgaaattct tttggttgaa ttacgcaaac
                                                                       480
aagcaaagga aaagtctcaa ttattattgg aaaatttggg gagagattat tatctcttga
                                                                       540
tctcctagtn natt
                                                                       554
      <210> 566
      <211> 631
      <212> DNA
     <213> Homo sapien
     <220>
     <221> misc feature
     <222> (1)...(631)
```

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<223> n = A, T, C or G

<213> Homo sapien

```
<400> 566
ncgaagctgt gaanncattc acacggaatc tgganggtat tactgtaact tcttataata
                                                                        60
cataatataa aagtttttga aagatataga cacaattaac ccctaaacaa cacactatct
                                                                        120
qattctcaaa aqcaatqqct atttaacaag atgtaaaagg acaataacat atcaaagaac
                                                                        180
tttcacacac ctaaagatag catttagcag caagttagtc agacaaaaca aacataaata
                                                                        240
tcttcacatt tcctatqttt qtttttaact ttacttcata aagccactga taattgaggt
                                                                        300
ttctttcaag tataagattt ctaaaattaa aaactgtttt tgacatattt ttataaagaa
                                                                        360
ataaaaagca aaacgcaatc caactattta tatgagtccc tcttctccaa cagctttaga
                                                                        420
tqtttttctq aqtacttttt acacagaata tttttattaa aatcagttct aattcattta
                                                                        480
tgcagattag gggaaaatga ttcataataa attaacttta aaattacctt ctatctgctt
                                                                        540
ctacctctat cccccatca ccaccaaatc tqttqctaca qtgaactgta gccaatgtct
                                                                        600
                                                                        631
gtttgagggg gcccaaagca tctggtaatc t
      <210> 567
      <211> 510
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(510)
      <223> n = A, T, C \text{ or } G
      <400> 567
                                                                         60
cctatnatag cttctctagc tatcatactc caatcagcna aaaatgagaa aatgttgaga
aatagaagat aatteeteat ttaaggneac ettetanaat ttgtgettaa nantetgttt
                                                                        120
tottotcatg ggccagcact toggcaactg ggaaaaatta ngngtacagg gatotaggna
                                                                        180
atactgttta tttgagcaat aatatattgn gctaacgttc aggcatccta ttactgagaa
                                                                        240
ataagggaaa atgagtgtaa agtacaacta agagtctcgg ctacagggaa aaataccatc
                                                                        300
                                                                      . 360
agttaaatat ccatagtcct agagcattta tgtaaaactg caatttgaat cctgcaatac
attttggctt tttcctcagt gataccatgt gtgggaagtt gttctgtcaa ggtgggtcgg
                                                                        420
ataatttgcc ctggaaagga cggatagtga ctttcctgac atgtaaaaca tttgatcctg
                                                                        480
aagacacaag tcaagaaata ggcatggtgg
                                                                        510
      <210> 568
      <211> 180
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(180)
      <223> n = A, T, C \text{ or } G
      <400> 568
                                                                         60
ttaatntgac ncacgcttat gcggaggaga atgntttcat gttacttata ctaacattag
                                                                        120
ttcttctata gggtgataga ttggtccaat tgggtgtgag gagttcagtt atatgtttgg
gattttttag gtagtgggtg ttgagcttga acgctttctt aattggtggc tgcttttagg
                                                                        180
      <210> 569
      <211> 237
      <212> DNA
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 agggatggga gggcgatgag gactaggatg atggcgggca ggatagttca gacggtttct
                                                                     120
 atttcctgag cgtctgagat gttagtatta gttagttttg ttgtgagtgt caggaaaagg
                                                                     180
 gcatacagga ctaggaagca gataaggaaa atgactatga gggcgtgatc atgaaag
                                                                     237
       <210> 570
       <211> 352
       <212> DNA
       <213> Homo sapien
      <400> 570
ctgtctctcc atttagagcc ccagttggtc ctgacctctt acaaatttgg tgttttcact
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 ttgatgttta tgaaccgatt gcattaaaaa tgcaggataa tgattcaggg ttagagaaac
                                                                     120
tattatttat acaaatgtgg ttaacacctc atcattttaa attggctgtg ctaataatgc
                                                                     180
tcattgtgct cttcagggtt atgtgtgtgt gtgtgtgtg gttttgcctg aatctgcaac
                                                                     240
ctacatttgc tctggcagta tgttgagtat atgctagaat agaatggacc taggcaactc
                                                                     300
taaggteeta caactaaata caettaetta ggaaaeetee taaataagta gg
                                                                     352
      <210> 571
      <211> 402
      <212> DNA
      <213> Homo sapien
      <400> 571
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                                                                     60
atattatact aagaaaagat acgactttat tttctggtag atagaaataa atagctatat
                                                                    120
ccatgtactg tagtttttct tcaacatcaa tgttcattgt aatgttactg atcatgcatt
                                                                    180
gttgaggtgg tctgaatgtt ctgacattaa cagttttcca tgaaaacgtt ttattgtgtt
                                                                    240
300
ccttgaggtc ttttgacatg tggaaagtga atttgaatga aaaatttaag cattgtttgc -
                                                                    360
ttattgttcc aagacattgt caataaaagc atttaagttg aa
                                                                    402
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      <211> 70
      <212> DNA
      <213> Homo sapien
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      <221> misc_feature
      <222> (1)...(70)
      <223> n = A,T,C or G
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ttttacaacq
                                                                     70
     <210> 573
     <211> 423
     <212> DNA
     <213> Homo sapien
     <400> 573
ccaatggttt cttagtgaaa gagtacacta gctctgaatg caatgccctc agaaagatat
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tcttcattca tgggatatcc gtattgtttc gttgaaattt	tgaccaacct atgctcactt taaaagaaca acatgtttga	ggctatagat gcattccttt gaaaataatc atctcaaagc	acatgacatt ttcagatgtc ccctttaatt ttggagcttt cacccatgtg actttgtatc	ctcttggctc tcattttcta gcttaagctt gaaagaaaac	gaaggatatc agtccttctt taatagcgat ttatgctctt	120 180 240 300 360 420 423
<212	> 574 > 129 > DNA > Homo sapie	en				
<400	> 574					
		gcaatatata	acagtttgct	aacaggattt	ttgactattc	60
		_	ttttactgag			120 129
<210:	> 575					
<211:	> 684					
<212	> DNA					
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<220:						
	· · misc_featu	ire				
	· (1)(684					
	n = A, T, C					
.400-	E7E					
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			ataaaacaca			120
			ttatttgcta			1.80
	-		gtctatggaa			240
	_	-	atgattgtat			300
			tgccactata			360
atagtttatt	tcaatttttt	ttcaactcat	acttccttta	aaatagcact	gaccaaaaga	420
			aatctttttg			480
			ccaagacata			540
			tttaaaatct			600
			tccagggctc	aatagtcacc	atgaatctca	660
attgtaatca	aagaggttgg	cctg				684
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· <211>	134		•			
	> DNA					
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		cgtacaggga	ggaatttgaa	gtagatagaa	accgacctgg	60
			gactttaatc			120
atagcggctg						134
<210>	. 577					
<21U2	- 111					

<211> 133

<212> DNA

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      <222> (1)...(133)
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tttgatgttt atgaaccgat tgcattaaaa atgcaggata atgattcagg gttaganaaa
                                                                     120
ctattattta tac
                                                                     133
      <210> 578
      <211> 200
      <212> DNA
      <213> Homo sapien
      <400> 578
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                                                                      60
cctggtaatt tcattcttta gtctctccaa gaaaatctga agtgtattag gcaagtcaga
                                                                     120
acceasattg tetecaaggt tgcaaataat ttgteecata caggaaatag ceettteett
                                                                     180
gacttcctga tcaatgtcag
                                                                     200
      <210> 579
      <211> 402
      <212> DNA
      <213> Homo sapien
      <400> 579
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                                                                      60
atattatact aagaaaagat acgactttat tttctggtag atagaaataa ataqctatat
                                                                     120
ccatgtactg tagtttttct tcaacatcaa tgttcattgt aatgttactg atcatgcatt
                                                                   .. 180
gttgaggtgg tctgaatgtt ctgacattaa cagttttcca tgaaaacgtt ttattqtqtt
                                                                     240
300
ccttgaggtc ttttgacatg tggaaagtga atttgaatga aaaatttaag cattgtttgc
                                                                     360
ttattgttcc aagacattgt caataaaagc atttaagttg aa
                                                                    402
      <210> 580
      <211> 245
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(245) ·
     <223> n = A, T, C \text{ or } G
     <400> 580
ccaattgatt tgatggtaag ggagggatcg ttgacctcgt ctgttatgta aaqqatqcqt
                                                                     60
agggatggga gggcgatgan gactaagatq atqqcqqqca qqataqttca qacnqtttct
                                                                    120
atttcctgag cgtctgagat gttagtatta gttagttttg ttgtgagtgt taggaaaagg
                                                                    180
gcatacagga ctaggaagca gataaagaaa atgactntta gggcgtgatc atnaaanggg
                                                                    240
ataaa
                                                                    245
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<211> 294 <212> DNA <213> Homo sapien					
<pre><400> 581 tgcagcgcaa gtaggtctac aagacgctac ttcccctatc atagaagagc ttatcacctt tcatgatcac gccctcatag tcattttcct tatctgcttc ctagtcctgt atgccctttt cctaacactc acaacaaaac taactaatac taacatctca gacgctcagg aaatagaaac cgtctgaact atcctgcccg ccatcatcct agtcctcatc gccctcccat ccctacgcat cctttacata acagacgagg tcaacgatcc ctcccttacc atcaaatcaa</pre>	60 120 180 240 294				
<210> 582 <211> 230 <212> DNA <213> Homo sapien					
<pre><400> 582 gaggtcgccc tcatagtcat tttccttatc tgcttcctag tcctgtatgc ccttttccta acactcacaa caaaactaac taatactaac atctcagacg ctcaggaaat agaaaccgtc tgaactatcc tgcccgccat catcctagtc ctcatcgccc tcccatccct acgcatcctt tacataacag acgaggtcaa cgatccctcc cttaccatca aatcaattgg</pre>	60 120 180 230				
<210> 583 <211> 481 <212> DNA <213> Homo sapien					
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<210> 584 <211> 306 <212> DNA <213> Homo sapien					
<pre><400> 584 ccaattaaga gctaaattta caaaataatc tctatcagga ggctttaagg tttaatgtct ctaaagtccc tatggatata agaggcttga atgtactgaa ttcaaatttg gttttaaat gttataatag tttaggcccg agagccacat atttctgtct aagaatagaa agcatagcta gctgcccaca cagaatattc atatagaggt ggggggcaag aacaaaattt attcatttga tacatagaaa tgggactact tagaatagac tcataataga aagcatcatc tggtttctca tctcag</pre> <pre><210> 585</pre>	60 120 180 240 300 306				
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<213> Homo sapien

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<400> 585
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 acatagaaaa acgtgtgcgg agtttgccag aaatagatgg cttgagcaaa gagacggtgt
                                                                        120
 tgagctcatg gatagccaaa tatgatgcca tttacagagg tgaagaggac ttgtgcaaac
                                                                        180
 agccaaatag aatggcccta agtgcagtgt ctgaacttat tctgagcaag gaacaactct
                                                                        240
 atgaaatgtt tcagcagatt ctgggtatta aaaaactaga acaccagctc ctttataatg
                                                                        300
catgtcag
                                                                        308
       <210> 586
       <211> 416
       <212> DNA
       <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(416)
      <223> n = A,T,C or G
      <400> 586
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                                                                        60
ctgaaaaatt ctaggaaagc ttattttccc ttatattttt atggnacttt caacacttna
                                                                       120
caacactatt tnaattaann tttnttctag agtttatann atatcagtac attctttct
                                                                       180
gtggatgcaa taatatagaa tottattnoa aatottactg gcaggntotn ttaaattott
                                                                       240
caacggntgn catagtgatt aaccaaaatt agttatgatt tctgcctatc tgtgtgagaa
                                                                       300
cttacagggg aaattgttct aaacctgagg aacatgaagt aactgtactg cacactccaa
                                                                       360
atgatgacag tcattttata tcaccttcaa ttacccaaca gcttttaata gtctgg
                                                                       416
      <210> 587
      <211> 382
      <212> DNA
      <213> Homo sapien
      <400> 587
cctactatgg gtgttaaatt ttttactctc tctacaaggt tttttcctag tgtccaaaga
                                                                        60
gctgttcctc tttggactaa cagttaaatt tacaagggga tttagagggt tctgtgggca
                                                                       120
aatttaaagt tgaactaaga ttctatcttg gacaaccagc tatcaccagg ctcggtaggt
                                                                       180
ttgtcgcctc tacctataaa tcttcccact attttgctac atagacgggt gtgctctttt
                                                                       240
agctgttctt aggtagctcg tctggtttcg ggggtcttag ctttggctct ccttgcaaag
                                                                       300
ttatttctag ttaattcatt atgcagaagg tataggggtt agtccttgct atattatgct
                                                                       360
tggttataat ttttcatctt tc
                                                                       382
      <210> 588
      <211> 307
      <212> DNA
      <213> Homo sapien
      <400> 588
cctactcttc tccgtccatt gtactatctg cccgtggtgg ggatggcagt aggatcatat
                                                                        60
ttgatgactt ccgagaagca tattattggc ttcgtcataa tactccagag gatgcgaagg
                                                                       120
tcatgtcctg gtgggattat ggctatcaga ttacagctat ggcaaaccga acaattttag
                                                                       180
tggacaataa cacatggact aatacccata tttctcgagt agggcaggca atggcgtcca
                                                                       240
cagaggaaaa agcctatgag atcatgaggg agctcgatgt cagctatgtg ctggtcattt
                                                                       300
ttggagg
                                                                       307
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<210> 589
      <211> 89
      <212> DNA
      <213> Homo sapien
      <400> 589
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                                                                        60
acagcaagac tgtctcaaaa aaaaaaaaa
                                                                        89
      <210> 590
      <211> 456
      <212> DNA
      <213> Homo sapien
      <400> 590
                                                                        60
cctcagttct tgattgtggt tgacggggcg tcaccatgaa ggagcccatt tagtataaag
                                                                       120
cttccaacct tttctcttaa tcgtttcttt aatcttttaa accatcttca agtgcatagg
ggagtttccg atgccagagg atgaaagcaa gtgctctctc caccctctcc tcccagagtg
                                                                       180
aaaacaaatc cttttgctga tacttgtttc aaaagcatcc attgtaaagc ttctcagtga
                                                                       240
cacaaaatac tgagaggtaa ctttttatca atcaaaccac ataccccaat ttaacacctt
                                                                       300
                                                                       360
tcaatgctct gaattcaact gacagactaa agggtgtttc ctgtaacagt ctgaaatatt
                                                                       420
aagtgttttt tttgttttgt ttttaaatct tatttcagaa aacttcctct tggggtagga
aagtacacat gaagcagcaa agtaacgaag aaaaac
                                                                       456
      <210> 591
      <211> 289
      <212> DNA
      <213> Homo sapien
      <400> 591
ccaattgatt tgatggtaag ggagggatcg ttgacctcgt ctgttatgta aaggatgcgt
                                                                        60
agggatggga gggcgatgag gactaggatg atggcgggca ggatagttca gacggtttct
                                                                       120
atttcctgag cgtctgagat gttagtatta gttagtttttg ttgtgagtgt taggaaaagg
                                                                       180
gcatacagga ctaggaagca gataaggaaa atgactatga gggcgtgatc atgaaaggtg
                                                                       240
ataagctctt ctatgatagg ggaagtagcg tcttgtagac ctacttgcg
                                                                       289
      <210> 592
      <211> 435
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(435)
      <223> n = A, T, C \text{ or } G
      <400> 592
                                                                        60
cgcgttagat gcgccttttc cggcctgtgc gtctgctctg gttcctctca ggcagcaaaag
ctggggaagg aagetcagge aggageetee eegacaceae ageggeacaa geageageta
                                                                       120
                                                                       180
aagcaccgca ctttgctctg ctaacctttt acttaaatga ggttttgcca aatccacatc
tggaaccgca tcacacccat ttgcaaggat gtttgttctt tgatgaaact gcatctctac
                                                                       240
                                                                       300
tgcacatgan ggctttcatt gtaggacaag aggagagttc gtttattttt gtaactgttt
tacatgttcc gattanttaa tcggnagctt atgtcatttg ctatgcctgt tgtcttctaa
                                                                       360
                                                                       420
tctctcctta ctaaaacatt acttcaaatt tnaattgacc cttgtttata atttatttaa
                                                                       435
cgggatttgn gtgtc
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<210> 593
       <211> 633
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc feature
       <222> (1)...(633)
       <223> n = A, T, C or G
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agcataaaat attatgaaac tattccagaa gttcagtaat atctttggga cctgctcata
                                                                        120
gcccaagttt tgtgaatact tttgtagtta aaaaaaattt ttactttacc agggcattgc
                                                                        180
aattetttte cateagtgaa ttteatteta cagaetttte agageatete ataateagte
                                                                        240
aacaaatcta tttcaaatgt gtttgttact aagcaacggt tgctaagagc ttctgtaatt
                                                                        300
aagatgaaag ttccaaggta acaatgccca aacacagcac cattttcacc attttctgat
                                                                        360
aatgcaggag taggatggct aaaagtgaaa gaagaatcta ctctatggaa agcatggcac
                                                                        420
ctgaaatttc tgaagatatt ggctgtcctc tagcttatat gagagagagt gtttgtgctt
                                                                        480
tactaatcaa ccagtcattt ttttcttgtg tggctgaaat gtacattcca gacatgaaca
                                                                        540
ggtagagtat gtgttggggg caggtttata ctgcatgggt gtgctgagac agggccacgt
                                                                        600
ggtgatgtaa atgatgctgn ctgacacgtg cag
                                                                        633
      <210> 594
      <211> 501
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(501)
      <223> n = A, T, C \text{ or } G
      <400> 594
cctttacaag atgctggtac cttgatcttg gacngggcag gctccaagat ggaaagaaag
                                                                         60
tgagcatctg ctttttaggg attatccagt ctatactact ctgttctagc cacacaaaac
                                                                       120
aggttaagac agaaattggt accaagagtg gggtgttact acagcaaata cctgaaaatg
                                                                       180
tagaagaggc tttgaaatgt ggtaattgga agaagctggt agaatttgga ggagtaggct
                                                                       240
agaaaatgtc tgtattttca tgaatggagc attaagaata attccggtga ggccataggg
                                                                       300
aaagtctaaa acttttcaga aattatgtaa gcgattgtga ttagtaggtt ggtagaaata
                                                                       360
tagacagtaa aagcaattct gatgtggttt cagaggaaaa tgaaaaatat tagaaactga
                                                                       420
aggaaggggc atccttgcta taaactggca aagaacttgg ctgaaatgtc tccatgtcca
                                                                       480
agagatttat ggcagaaatg t
                                                                       501
      <210> 595
      <211> 383
      <212> DNA
      <213> Homo sapien
      <400> 595
ctggtcacca tcatcccttt aatcaactca cacctgttta aagagtgttt ctgatttgac
                                                                        60
cttcatccct tagtttactg gcgttaaaaa aagtctcagc aattttcatt atttctcgtg
                                                                       120
ggtctcatta tcaaaccttt acttatttcg gcatatttcc tctgggcttc ttctagtttc
                                                                       180
tgccttacaa gcaatgctgt tctgtaaatt tattgaaacc tctggaacat ttcaccttta
                                                                       240
```

```
gagatggagg atggaaggat tggtaccaga agagggctaa gatacgtttt ctgtcttgag
                                                                  300
                                                                  360
ctgaaagcac agtctactct ccttcgtttt gtcgatgaga aagttgaggc cagaggggag
gtgacatgtt tagagtcacc cag
                                                                  383
     <210> 596
     <211> 266
     <212> DNA
     <213> Homo sapien
     <400> 596
                                                                  60
120
ggaggttagt tgtggcaata aaaatgatta aggatactag tataagagat caggttcgtc
ctttagtgtt gtgtatggct atcatttgtt ttgaggttag tttgattagt cattgttggg
                                                                  180
tggtaattag tcggttgttg atgagatatt tggaggtggg gatcaataga gggggaaata
                                                                  240
                                                                  266
gaatgatcag tactgcggcg ggtagg
     <210> 597
     <211> 383
     <212> DNA
     <213> Homo sapien
     <220>
     <221> misc feature
     <222> (1)...(383)
     <223> n = A, T, C \text{ or } G
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ctggtcacca tcatcccttt aatcaactca cacengttta aagagtgttt ctgatttgac
                                                                  60
cttcatccct tagtttactg gcgttaaaaa aagtctcagc aattttcatt atttctcgtg
                                                                  120
                                                                  180
ggtctcatta tcaaaccttt acttatttcg gcatatttcc tctgggcttc ttctagtttc
                                                                  240
tgccttacaa gcaatgctgt tctgtaaatt tattgaaacc tctggaacat ttcaccttta
                                                                  300
qaqatqqaqq atqqaaqqat tggtaccaga agagggctaa gatacgtttt ctgtcttgag
ctgaaagcac agtctactct ccttcgtttt gtcgatgaga aagttgaggc cagaggggag
                                                                  360
                                                                  383
gtgacatgtt tagagtcacc cag
     <210> 598
     <211> 266
     <212> DNA
     <213> Homo sapien
     <400> 598
                                                                  60
ggaggttagt tgtggcaata aaaatgatta aggatactag tataagagat caggttcgtc
                                                                  120
                                                                 180
ctttagtgtt gtgtatggct atcatttgtt ttgaggttag tttgattagt cattgttggg
tggtaattag tcggttgttg atgagatatt tggaggtggg gatcaataga gggggaaata
                                                                 240
                                                                 266
gaatgatcag tactgcggcg ggtagg
     <210> 599
     <211> 294
     <212> DNA
     <213> Homo sapien
     <220>
     <221> misc_feature
     <222> (1)...(294)
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\langle 223 \rangle n = A,T,C or G
       <400> 599
 ccaattgatt tgatggtaag ggagggatcg ttgaccacgt ctgttatgta aaggatgcgt
                                                                         60
 agggatggga gggcgatgag gactaggatg atggcgggca ggatagttca gacggtttct
                                                                         120
 atttcctgag cgtctgagat gttagtatta gttagttttg ttgtgagtgt taggaaaagg
                                                                         180
gcatacagga ctaggaagca nataaggaaa atgactatga gggcgtgatc atgaaaggtg
                                                                         240
 ataagetett etatgatagg ggaagtageg tettgtagae etaettgege tgea
                                                                         294
       <210> 600
       <211> 213
       <212> DNA
       <213> Homo sapien
       <400> 600
agatattggg ctgttaattg tcagttcagt gttttaatct gacgcaggct tatgcggagg
                                                                          60
agaatgtttt catgttactt atactaacat tagttcttct atagggtgat agattggtcc
                                                                         120
aattgggtgt gaggagttca gttatatgtt tgggattttt taggtagtgg gtgttgagct
                                                                         180
tgaacgcttt cttaattggt ggctgccttt agg
                                                                         213
      <210> 601
      <211> 471
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(471)
      <223> n = A,T,C or G
      <400> 601
ncctactatg ggtgttaaat tttttactct ctctacaagg ttttttccta gtgtccaaag
                                                                         60
agctgttcct ctttggacta acagttaaat ttacaagggg atttagaggg ttctgtgggc
                                                                        120
aaatttaaag ttgaactaag attctatctt ggacaaccag ctatcaccag gctcggtagg
                                                                        180
tttgtcgcct ctacctataa atcttcccac tattttgcta catagacggg tgtgctcttt
                                                                        240
tagctgttct taggtagctc gtctggtttc gggggtctta gctttggctc tccttgcaaa
                                                                        300
gttatttcta gttaattcat tatgcagaag gtataggggt tagtccttgc tatattatgc
                                                                        360
ttggttataa tttttcatct ttcccttgcg gtactatatc tattgcgcca ggtttcaatt
                                                                        420
tctatcgcct atactttatt tgggtaaatg gtttggctaa ggttgtctgg t
                                                                        471
      <210> 602
      <211> 482
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(482)
      <223> n = A, T, C \text{ or } G
      <400> 602
tgagcataca gcaataaaaa taacataatt tntatgtgta caatatttat ggaatacgtt
                                                                         60
actggaacag ataaataatt tagttaataa catgacaaag aacagaaatt gtatacacta
                                                                        120
tacagcatag taatagaata atgaatgatt aaagttatta atattaggta gaaaatgaag
                                                                        180
ggtatctttg agagcagaac tcaaggaagc aagcaatttg ccttatgagg aaagagttac
                                                                        240
```

ctgtggataa aggagaaact gaaaaattta caagtcaaga ctttttgagc aaaaacaaaa atatgactat gagtcaccaa ttcagtacag tgaaaaaaaa gttgaagaga tatcttggaa gtaaaccatg ttgtggaaga gcagggtttt gataatcatg ggattattct gaatgaattt taaatgcgat aggaatatat gagataattt caccagagaa taatatgatc atgtttgcat tt	300 360 420 480 482
<210> 603 <211> 372 <212> DNA <213> Homo sapien	
<400> 603 gttccaacct tcatttctga aactgttcta gagcactttg tctttctcgt agttcataac	60
ttaccccttc agtctagaat tagaattaca ttatctgttt tactacttta ctagactgta	120
agctcctaga agataaggac tagggagttc atctctgtat tccaccagaa ggtacagtga ctcataacta gagtctttag atgaaactta ctgagttgaa taacttaata tatttctgtt	180 240
ttcattccca agggaggcca tgtctggaga tagaccttga atttaataaa ttttaggcac	300
tataccattt cagtggagaa aattgttggg aaatttgggg ggatggat	360
ggaagtcact gg	372
<210> 604	
<211> 468	
<212> DNA	
<213> Homo sapien	
<220>	
<221> misc_feature	
<222> (1)(468) <223> n = A,T,C or G	
(223) 11 - A,1,0 01 0	
<400> 604	:
gengtitiga gigagitiet taateetgag tietggniig attgeactgi ggietgagag	60 120
atagtttgtt ataatttctg ttcttttaca cttactgagg agagctttac ttccaagtat. gtggtcgatt ttggaatagg tgtggtgtcg tgctgaaaag aatgtatatt ctgttgattt	180
ggggtggaga gttctgtana tgtctattag gtccgcttgg tgcagagttg agttcaattc	240
ctggatagcc ttgttaactt tctgtctcgt tgatctgtct aatgttgaca gtggggtggt	300
aaagtctccc attattattg tgtgggagtc taagtctctt tgtaggtcac taaggacttg	360
ctttatgaat ctgggtgctc ctgcattggg tgcacatata tttaggacag cnagctcttc	420 468
ttgttgaatt gatcccttta ccattatgta atggccttgn ctcttttg	400
<210> 605	
<211> 288	
<212> DNA	
<213> Homo sapien	
<400> 605	
ccaattgatt tgatggtaag ggagggatcg ttgacctcgt ctgttatgta aaggatgcgt	60 120
agggatggga gggcgatgag gactaggatg atggcgggca ggatagttca gacggtttct atttcctgag cgtctgagat gttagtatta gttagttttg ttgtgagtgt taggaaaagg	180
gcatacagga ctaggaagca gataaggaaa atgactatga gggcgtgatc atgaaaggtg	240
ataagctctt ctatgatagg ggaagtagcg tcttgtagac ctacttgc	288
210, 606	
<210> 606	

<211> 572

<212> DNA

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<213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(572)
       <223> n = A,T,C \text{ or } G
       <400> 606
gaatnaaatg aatgaaatag aaaatataat tgagagcttc aacaacagac tataccaaat
                                                                         60
ggaggaaaaa atttctgaac ttgaagatag atcttttgaa ataacacaag cagtggcaaa
                                                                        120
aatgaattaa aaagaataag gaaagcctaa aggatttatg agatatcatt aagcaagcaa
                                                                        180
atattcatac tatgggcatt ccagatggaa aaaagaaggg taaaggtgag gaaatcatat
                                                                        240
ttaatgaaat aatagcagaa aatttccgga gtcttgggag agagatgagc atttaggtcc
                                                                        300
agggagetea aagaaceeea aacagattea acceaaacag gteetetetg gageecaaca
                                                                        360
tagtcaaatt gtaataagta aaagacaaag aattccaana agcattcaag agaaaagagt
                                                                        420
caagtcataa ataagggaat ctccattagg ctaacagcag atatctcagc agaaagctta
                                                                        480
cangccanga gagaatggga tgatatattc aaagtacttg aaagcagggg tnggggaaac
                                                                        540
cctgctagct aaaaatatta tacccttgca aa
                                                                        572
      <210> 607
      <211> 178
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(178)
      <223> n = A, T, C or G
      <400> 607
ctcggggtaa tctcccagca agaggtcagg tcctggntgt gcgtcccagg gtgtcagtga
                                                                         60
aattggctgc tcccctgacc cagggcacct tcatgcgtct tcacagcagg actactgtga
                                                                        120
ccaaggccag acctttcatc tttcaaaaga ctttgactaa aaatgcttta aaaaagca
                                                                        178.
      <210> 608
      <211> 416
      <212> DNA
      <213> Homo sapien
      <400> 608
cctgtctttg aatggatgaa ataggttaat aaagaacatc actgtttaaa aactagaaca
                                                                        60
ctgaaaaatt ctaggaaagc ttattttccc ttatattttt atggtacttt caacacttaa
                                                                       120
taacactatt tcaattaagt tttctcctag agtttatagt atatcagtac attcctttct
                                                                       180
gtggatgcaa taatatagaa tettatteea aatettaetg geaggttete ttaaattett
                                                                       240
caacggctgt catagtgatt aaccaaaatt agttatgatt tctgcctatc tgtgtgagaa
                                                                       300
cttacagggg aaattgttct aaacctgagg aacatgaagt aactgtactg cacactccaa
                                                                       360
atgatgacag tcattttata tcaccttcaa ttacccaaca gcttttaata gtctgg
                                                                       416
      <210> 609
      <211> 648
      <212> DNA
      <213> Homo sapien
      <400> 609
ctgatctctc agcagaaact cttcaaacca gaagagagtg ggggccaata ttcaacattc
                                                                        60
```

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ttaaagaaaa taattttcaa cccagaattt catatccagc caaactaacc ttcacaagtg
                                                                        120
aaggagaaat aaaatccttt acagacaagc aaatgctgag agattttatc accaccaggc
                                                                        180
ctaccctaaa agagttcctg aaggaagcac taaacatgga aaggaacaac cagtaccatc
                                                                        240
gaggctagga agaaaccgca tcaactaagg agcaaaataa ccagctaaca tcataatgac
                                                                        300
aggatcagat tcacacataa cgatattaac tttaaatgta aatggactaa atgctccaat
                                                                        360
taaaaqacac aqactqqcaa attqqataaa qaqtcaaqac ccatcaqqqt gctgtattca
                                                                        420
qqaaacccat ctcaccqtqc aqaqacacac ataggctcaa aataaagggc tggaggaaga
                                                                        480
                                                                        540
tctaccaagc aaatggaaaa caaaaaaagg caggggttgc aatcctagtc tctgataaaa
cagactttaa accaacaaag atcagaagag acaaagaagg ccattacata atggtaaagg
                                                                       600
gatcaattca acaagaagag ctaactatcc taaatatata ttgcaccc
                                                                        648
      <210> 610
      <211> 310
      <212> DNA
      <213> Homo sapien
      <400> 610
ccagetette tetgteacat tectatttet gaettetgee tggettteag tttetgeece
                                                                         60
accttggctt tttcccagct tgaacctaat agaactccag agtttggggg gaggcccagc
                                                                        120
cctttgtttt ctgctcttga agcatattca cacataaaaa gttgtattct cttacacaaa
                                                                        180
ctqttttqaq qctcttaccq taqtcqaaqg tatcttagat cttccttagt gatctcatta
                                                                        240
                                                                        300 -
aqaatatccq aaaqtqtata accetettea acaatetgaa acaaagatea gateettaag
                                                                        310
agctgagcag
      <210> 611
      <211> 254
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(254)
      <223> n = A, T, C \text{ or } G
      <400> 611
                                                                         60
ctgtttttac atctaaagca atagactaga actgaattnt cttctacata gtaaaatcac
                                                                        120
aattgtggaa ttacaggaat tctggtgata ttaaggtgaa acaacaaaac acaaaaggcc
                                                                        180
ctattttaac agttgatgtg acagtaagtt ttaatagaac ctgtaacttc attttggaaa
tgcttctcca ccaaataagg cctttttccc ctatttaagg agccagatgg attgaaagat
                                                                        240
                                                                        254
gtggaaatag gcag
      <210> 612
      <211> 225
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(225)
      <223> n = A, T, C \text{ or } G
      <400> 612
                                                                         60
ctgactatat catqtcacca tcatagccaa tacaacattn ttgccatact tcctaaaaaac
cttttcqcat acactgatca tgctacttat cagcactttc taacatcctg accaaacaga
                                                                        120
cacccacacc tcttatagag tacactgtga gagaataaca tggacttgat atggcatcac
                                                                        180
```

```
225
      <210> 613
      <211> 471
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(471)
      <223> n = A,T,C or G
      <400> 613
ccatcagact tcttgggtgc ctggctatat tcaatgtgaa gtaaaaaata tcccaagtct
                                                                      60
tacaccaaaa tagaggctct gacttagaag tatgctttta gctttcttt taaataagac
                                                                     120
attctggaag aaaaaaaag aaaaaggaaa gaaaatcaag tttgaaacac agttaacact
                                                                     180
tattttggca agaaagcaac caaaatctaa aaagcataaa ctatgngtcc aaatgnaaaa
                                                                     240
ggnattacag aacaaactgc aagaggggaa aattaaagcc ncactgaacg aaaaaataca
                                                                     300
gtatgtctaa cattttgqaa ttgnaattta aaccctaaqq qcaaaaqctg aaaaatcatq
                                                                     360
cttanacctn ggncgngacc acnctaaggg cgaattccan cacactggcg gncgttacta
                                                                     420
gtggatccna nctcggtacc aagcttggcg taatcctngg catagctgtt t
                                                                     471
      <210> 614
      <211> 421
      <212> DNA
      <213> Homo sapien
      <400> 614
gttatttttt agaatggctc tcccatcttg agtatgtgtg atgtttcctc atgtatgaat
                                                                     60
gaagcatata catctttqtc agaaqtatcc caqaaqcaat tctqtactct cctcattatq
                                                                     120
ttctattggg tgggccatgg tttttgattt gtctcattac tgatgatggt tacttttatt .
                                                                     180
atttgataaa ggttgtatat aacttatcta ttatggcata atacattagc taaaaccttg
                                                                     240
gcggtgtaaa acagcagata cttacgtttc tcataggaat ggctctattg agtacctctq
                                                                     300
tctcaaggct tctcaagagt ttgtagctac cttgttggct ggggttgcgg tctgacctaa
                                                                     360
aggettagtt agggggtggt agaaatette catatgttet ttgetaegtg gaceteacag
                                                                     420
g
                                                                     421
     <210> 615
     <211> 242
     <212> DNA
     <213> Homo sapien
     <400> 615
cctcctattt attctagcca cctctagcct agccgtttac tcaatcctct qatcaggatg
                                                                     60
agcatcaaac tcaaactacg ccctgatcgg cgcactgcga gcagtagccc aaacaatctc
                                                                     120
atatgaagtc accctagcca tcattctact atcaacatta ctaataagtq qctcctttaa
                                                                     180
cctctccacc cttatcacaa cacaagaaca cctctgatta ctcctgccat catgaccctt
                                                                     240
gg
                                                                     242
     <210> 616
     <211> 392
     <212> DNA
     <213> Homo sapien
```

<220>

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<221> misc feature
      <222> (1)...(392)
      <223> n = A, T, C \text{ or } G
      <400> 616
cctaatttqt aqattqtqaa agcagctttt agtttaactt atttacagac cccttataat
                                                                         60
taccatgttt tttttttnt tcctaaatct nttggttcag cttgngaatn ttacgtgccc
                                                                        120
gtaaagtngg gatgttgaat nggcccttnt ttgttctggc agngagtcaa gngtccanca
                                                                        180
ttttttcata agngtttttt aaaatngttc tccancattt tatggctcct ccctcccatg
                                                                        240
tcctcaaacc cagcaaaagc gtanaggcan aattanagga cccncccggg cggccgntaa
                                                                        300
gggcnaattc cagcncactg gcggccgtta ctagnggatc cnagctcggn nccaagctng
                                                                        360
gcgtaatcat ggncatagct gtttcctgtg an
                                                                        392
      <210> 617
      <211> 215
      <212> DNA
      <213> Homo sapien
      <400> 617
cctactatgg gtgttaaatt ttttactctc tctacaaggt tttttcctag tgtccaaaga
                                                                         60
gctgttcctc tttggactac cagttaaatt tacaagggga tttagagggt tctgtgggca
                                                                        120
                                                                        180
aatttaaagt tgaactaaga ttctatcttg gacaaccagc tatcaccagg ctcggtaggt
                                                                        215
ttgtcgcctc tacctataaa tcttcccact atttt
      <210> 618
      <211> 433
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(433)
      <223> n = A, T, C \text{ or } G
      <400> 618
cttttgtntg cctgttttgt ggactggctg gctctgttag aactctgtcc aaaaagtgca
                                                                         60 .
tggaatataa cttgtaaagc ttcccacaat tgacaatata tatgcatgtg tttaaaccaa
                                                                        120
                                                                        180
atccaqaaaq cttaaacaat aqaqctgcat aatagtattt attaaagaat cacaactgta
aacatgagaa taacttaagg attctagttt agttttttgt aattgcaaat tatatttttg
                                                                        240
ctqctqatat attaqaataa tttttaaatg tcatcttgaa atagaaatat gtattttaag
                                                                        300
cactcacgca aaggtaaatg aacacgtttt aaatgtgtgt gttgctaatt ttttccataa
                                                                        360
                                                                        420
gaattgtaaa cattgaactg aacaaattac ccataatgga tttggttaat gacttatgag
                                                                        433
caagctggtt tgg
      <210> 619
      <211> 259
      <212> DNA
      <213> Homo sapien
      <400> 619
                                                                         60
ctgcagtgtc cctttttata tcatgctagt gttgagacat acttgactaa cttgggaaca
gttcgatata ttgacaaccg tcaacttaag aaaatcaaca gcttttggcc ccagcgtcca
                                                                        120
agtgaacttt tcatggagtg cagaatctca aatggacaaa atactttgtc tttttaaata
                                                                        180
                                                                        240
ctgaaaattt aattattagt actatgactg aaagattett catggetaaa aagetetgea
                                                                        259
tcaaactcaa ttcaggagg
```

<211> 489

```
<210> 620
       <211> 393
       <212> DNA
       <213> Homo sapien
       <400> 620
ccaccaaagc cacacggaga ttctgtcagg cgctgagaca ccacagcctt ttcaatctta
                                                                         60
gggaaagaaa tcaagtcata taaattaata tcaacaggta aggtcattga gcaattgtct
                                                                        120
ttcaactgtc taagacttta tcacttaaga tcataaacac agaagcaggt cataaaaata
                                                                        180
gcttttctta aggtttagga gaatttgtag gggcacttac ttgataatct gaattttcta
                                                                        240
gtcagaagtt taaataccac cttttaaaaaa cataaaattt aatttgtaac aagttattaa
                                                                        300
caaagcagta ttgtcgaaag ttttaagctt tctcccaata atttaattac attaattaaa
                                                                        360
tttttaccat tctaatggtt acaaaqtaac cag
                                                                        393
      <210> 621
      <211> 563
      <212> DNA
      <213> Homo sapien
      <400> 621
ctgacaatga taaaattatc tctatatggg caaacgcgtg ctctttgtcg aagaagaaag
                                                                        60
cttcagcttc atgttccagg tgagttaatt aggcaatgta tgaatgctaa tatctctttc
                                                                       120
acatattttg cttaagatct gtcttaggac tctcgtctgg cccatatggt tttccaaggg
                                                                       180
cagaagggcc tctttttgat gagaggcagt tttcagtaac tcttaaagtg ataacagcaa
                                                                       240
aggagaggag agagaagagt aagacaaatc gaaacattct tcaattgctt cttggccttt
                                                                       300
tggctaagct caagctcaaa acaggtcttc aaggagaaaa tacatcacaa agaaaaggat
                                                                       360
gttttatttc ttaccttgtc ctagaaaaat ttccataaac tctattggct taattctgta
                                                                       420
aacttgacca atatcagagt gcttcctacc aaggagggta gctgatgagc gtgaccatgg
                                                                       480
tacatcctag aagaatgtgt gatgaagaag ctttcaccgt gtaaaagagt tgaaaattat
                                                                       540
tcaaggagac attatggtct tgg
                                                                       563
      <210> 622
      <211> 505
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(505)
      <223> n = A,T,C or G
      <400> 622
tcttaagtgt gtttaataga taaagtaaac tttcctagtc aagggttaga tttttattat
                                                                        60
ctcttgtgtt ccgactttct acttttcaac tttgaacttc aaaaaaacat tactttgctt
                                                                       120
atcctttgta ctttgatcag gttgtttaga attgtagatc aaaccattct ttgatcattt
                                                                       180
tattgtttaa atgnttagtt ccatttataa tttttatagc caactctcgg ttatttctgt
                                                                       240
cttttgagat tgcaattcag aagctgtatg tcgaagtaat ttatgagttg acttttatac
                                                                       300
ttaggcttct ttaaatacta atagtcaaga attctagagc atctaataaa aaattaactt
                                                                       360
tcagatcatt gggaatctgt cctcatttaa atatgtgtaa atgcatttcc acagcaaatt
                                                                       420
gcttcatgcc ctttgnctat aaggaaatta ttccttgtag ctaatacatt tttcattttg
                                                                       480
cagnccaaat ctttttgag aaagg
                                                                       505
      <210> 623
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202

<212> DNA <213> Homo sapien

<400> 623 60 cctactatgg gtgttaaatt ttttactctc tctacaaggt tttttcctag tgtccaaaga gctgttcctc tttggactaa cagttaaatt tacaagggga tttagagggt tctgtgggca 120 aatttaaagt tgaactaaga ttctatcttg gacaaccagc tatcaccagg ctcggtaggt 180 240 ttgtcgcctc tacctataaa tcttcccact attttgctac atagacgggt gtgctctttt agetgttett aggtageteg tetggttteg ggggtettag etttggetet eettgeaaag 300 ttatttctag ttaattcatt atgcagaagg tataggggtt agtccttgct atattatgct 360 tggttataat ttttcatctt tcccttgcgg tactatatct attgcgccag gtttcaattt 420 ctatcgctat actitatitg ggtaaatggt tiggctaagg tigtciggta gtaaggigga 480 489 gtgggtttg <210> 624 <211> 233 <212> DNA <213> Homo sapien

<400> 624 gttggggaac agctaaatag gttgttgttg atttggttaa aaaatagtag ggggatgatg 60 ctaataatta ggctgtgggt ggttgtgttg attcaaatta tgtgtttttt ggagagtcat 120 180 gtcagtggta gtaatataat tgttgggacg attagtttta gcattggagt aggtttaggt 233 tatgtacgta gtctaggcca tatgtgttgg agattgagac tagtagggct agg

<210> 625 . <211> 459 <212> DNA <213> Homo sapien

<400> 625 ttcgagaaca tttttaataa ataatgtgac aaaattactt ttctgattat tggattttca 60 gtatgcaaaa ttatggctaa aaataagggg cttcttacat gaacataatg aaaacattaa 120 tcacatggat tgttccctta gtactgcacg ccttttctat ggaacttttt caaattatct 180 240 aaatgaacaa gtttggtttt ggtgaacacc agcctttttt ttttgtggttc agttttgttt 300 ggctttgtct tccactgggg tcagacctga tacttatcta tctatgaata aatgtacatt tttttcttca aataqcacca attataaaat caatgatatt cataaaatga caaaaaagga 360 tcatagaaat ctactagtca gagggcatca tttgtcaatt gaaagcaagt aatgcctcta 420 ttagagattt taaggaaatc ttgtaggttt cgacattgg 459

<210> 626 <211> 458 <212> DNA <213> Homo sapien

<400> 626

60 cctgatgatt gttttaaaca gtagaaaggg ttcagctaag aactacagtc cactctcagc 120 cctgtcatgt actataggac aagtcttcat tcacaacaaa tggatagcaa caccaatctc gtaacactgg gaaaactgca tacaatattt agaaggaaca ctaatacagc agaatctgca 180 240 cacaacggag tcaaagatct gaggccaaat cctactacac tttacgactt tgagttggtc 300 acttttctga accttagctt ctccatcagt gtaaaactga tgtaaaataa tataaagcta 360 tatgaaagct gatgtgattt acttgtgaaa tagtatgtgc aaaaggactt tgtaaaatgt 420 458 caagcattca tttagagtca tgtgcaaggc actgtgct

```
<210> 627
      <211> 393
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(393)
      <223> n = A, T, C or G
      <400> 627
ccatnngaac gcactcagga ggtggtttgt tctggatgca gaaaccagag atctagtttc
                                                                         60
tatccacaca gacgggaatg aacagctctc tgtgatgcgc tactcaatag atggtacctt
                                                                        120
cctggctgta ggatctcatg acaactttat ttacctctat gtagtctctg aaaatggaag
                                                                        180
aaaatatagc agatatggaa ggtgcactgg acattccagc tacatcacac accttgactg
                                                                        240
gtccccagac aacaagtata taatgtctaa ctcgggagac tatgaaatat tgtactggga
                                                                        300
cattccaaat ggctgcaaac taatcaggaa tcgatcggat tgtaaggaca tttgattgga
                                                                        360
ccgacatata cctgtgggct aggacttcca gga
                                                                        393
      <210> 628
      <211> 233
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(233)
      <223> n = A, T, C or G
      <400> 628
ctggatttat aaaatagttg aatgacaaaa gaagnntgtt ttgacagtaa aaaaaagaca
                                                                         60
ttatggacaa aatatgcaaa atgtgcaaag aaaaaataaa tttgcattag aaaggtgggc
                                                                        120
atttgatete tgagecetgt gecatgtaac attgecatgt tettteactg ttgtttgaat
                                                                        180
gttgtacccc ancccttgac tctggactta aggcaagcta tgactggctt tgg
                                                                        233
      <210> 629
      <211> 450
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(450)
      <223> n = A,T,C \text{ or } G
      <400> 629
                                                                        60
conggacaat ntaggoagga gaaggaaata aagggtatto aattaggaaa agaggaagto
aaattgtccc tgtttgcaga tgacatgatt gtatatctag aaaaccccat tgcctcagcc
                                                                       120
caaaatctcc ttaagctgat aagcaactcc agcaaagtcg caggatacaa aatcaatgga
                                                                       180
cacaaatcac aaacattctt atacaccaat aacagacaaa cagaggccaa atcacgagtn
                                                                       240
qaactctatt ccaattgctt tcaagaaaat taaaatacct aqqqatccaa cttacaaggg
                                                                       300
acatgaagga cctcttcaag gagaaactac aaaccactgc tcaatgaaat aaaagaggat
                                                                       360
acaaagaaat ggaagaacat tccatgctca ttggtagctt gatggggatg gcattgaatc
                                                                       420
tataaattac cttgggcagt atggacctca
                                                                       450
```

```
<210> 630
      <211> 486
      <212> DNA
      <213> Homo sapien
      <400> 630
cctactatqq qtqttaaatt ttttactctc tctacaaggt tttttcctag tgtccaaaga
                                                                         60
gctgttcctc tttggactaa cagttaaatt tacaagggga tttagagggt tctgtgggca
                                                                        120
aatttaaagt tgaactaaga ttctatcttg gacaaccagc tatcaccagg ctcggtaggt
                                                                        180
ttqtcqcctc tacctataaa tcttcccact attttqctac atagacgggt gtgctctttt
                                                                        240
agctqttctt agqtagctcq tctggtttcg gqqgtcttag ctttggctct ccttgcaaag
                                                                        300
ttatttctag ttaattcatt atgcagaagg tataggggtt agtccttgct atattatgct
                                                                        360
tggttataat ttttcatctt tcccttgcgg tactatatct attgcgccag gtttcaattt
                                                                        420
ctatcgccta tactttattt gggtaaatgg tttggctaag gttgtctggt agtaaggtgg
                                                                        480
                                                                        486
agtggg
      <210> 631
      <211> 211
      <212> DNA
      <213> Homo sapien
      <400> 631
tttacataaa tattatacta gcatttacca tctcacttct aggaatacta gtatatcgct
                                                                        60
cacacctcat atcctcccta ctatgcctag aaggaataat actatcactg ttcattatag
                                                                        120
ctactctcat aaccctcaac acccactccc tcttagccaa tattgtgcct attgccatac
                                                                        180
                                                                        211
tagtetttge egeetgegat geageggtag g
      <210> 632
      <211> 293
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(293)
      <223> n = A,T,C \text{ or } G
      <400> 632
cagegeaagt aggtetacaa gaegetactt cecetateat agaagagett atcacettte
                                                                        60
atgatcacgc cctcatagtc atttttcctt atctgcttcc tagtcctgta tgcccttttc
                                                                        120
ctaacactca caacaaaact aactaatact aacatctcag acgctcagga aatagaaacc
                                                                        180
gtctgaacta ngctgcccgc catcatccta gtcctcatcg ccctcccatc cctacgcatc
                                                                        240
                                                                        293
ctttacataa caqacqaggt cnacgatccc tcccttacca tcaaatcaat tgg
      <210> 633
      <211> 263
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (263)
      <223> n = A, T, C or G
      <400> 633
```

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nggtctgcag tgtccctttt tatatcatgc tagtgttgag acatacttga ctaacttggg
                                                                        60
aacagttcga tatattgaca accgtcaact taagaaaatc aacagctttt ggccccagcg
                                                                       120
tccaagtgaa cttttcatgg agtgcagaat ctcaaatgga caaaatactt tgtcttttta
                                                                       180
aatactgaaa attnaattat tagtactatg actgaaagat tottcatggc taaaaagctc
                                                                       240
tgcatcaaac tcaattcagg agg
                                                                       263
      <210> 634
      <211> 491
      <212> DNA
      <213> Homo sapien
      <400> 634
cctactatgg gtgttaaatt ttttactctc tctacaaggt tttttcctag tgtccaaaga
                                                                        60
gctgttcctc tttggactaa cagttaaatt tgcaagggga tttagágggt tctgtgggca
                                                                       120
aatttaaagt tgaactaaga ttctatcttg gacaaccagc tatcaccagg ctcggtaggt
                                                                       180
ttgtcgcctc tacctataaa tcttcccact attttgctac atagacgggt gtgctctttt
                                                                       240
agctgttctt aggtagctcg tctggtttcg ggggtcttag ctttggctct ccttgcaaag
                                                                       300
ttatttctag ttaattcatt atgcagaagg tataggggtt agtccttgct atattatgct
                                                                       360
tggttataat ttttcatctt tcccttgcgg tactatatct attgcgccag gtttcaattt
                                                                       420
ctatcgccta tactttattt gggtaaatgg tttggctaag gttgtctggt agtaaggtgg
                                                                       480
agtgggtttg g
                                                                       491
      <210> 635 '
      <211> 270
      <212> DNA
      <213> Homo sapien
      <400> 635
ccaattgatt tgatggtaag ggagggatcg ttgacctcgt ctgttatgta aaggatgcgt
                                                                        60
agggatggga gggcgatgag gactaggatg atggcgggca ggatagttca gacggtttct
                                                                       120
atttcctgag cgtctgagat gttagtatta gttagttttg ttgtgagtgt taggaaaagg
                                                                       180
gcatacagga ctaggaagca gataaggaaa atgactatga gggcgtgatc atgaaaggtg
                                                                       240
ataagctctt ctatgatagg ggaagtagcg
                                                                       270
      <210> 636
      <211> 383
      <212> DNA
      <213> Homo sapien
      <400> 636
cctactatgg gtgttaaatt ttttactctc tctacaaggt tttttcctag tgtccaaaga
                                                                        60
gctgttcctc tttggactaa cagttaaatt tacaagggga tttagagggt tctgtgggca
                                                                       120
aatttaaagt tgaactaaga ttctatcttg gacaaccagc tatcaccagg ctcggtaggt
                                                                       180
ttgtcgcctc tacctataaa tcttcccact attttgctac atagacgggt gtgctctttt
                                                                       240
agctgttctt aggtagctcg tctggtttcg ggggtcttag ctttggctct ccttgcaaag
                                                                       300
ttatttctag ttaattcatt atgcagaagg tataggggtt agtccttgct atattatgct
                                                                       360
                                                                       383
tggttataat ttttcatctt tcc
      <210> 637
      <211> 537
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
```

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```
<222> (1)...(537)
      \langle 223 \rangle n = A,T,C or G
      <400> 637
                                                                       60
ttttaatcct ggggtatata ggcagnactt taaattgcaa agtcttccgg gcctattttc
                                                                      120
ctctacattt ttqtaattaa ctctgggggc ttacttgttt tggcagtact gaaatcaaag
qaqctqqttc ttctttctc ccaattattt tcatatgaaa gcacctacaa ttagcctgtt
                                                                      180
agtcctattc agatacatca aatatcagtg aatgctttac tattcgcaca tttaagcatc
                                                                      240
                                                                      300
tttgttttac ataaaattag agtatgaaaa ccagtgttca attttttatc ttgttgagct
tgtaaaatgc cagcaattta aaactaggac ttttcccccc ataagccaag gaggtagaat
                                                                      360
                                                                      420
tactaataca agggttaaag aaggtagatt ttgttttcaa tatttgggta atattagaaa
                                                                      480
gattetteee acagggaaga actagcaagt gteecaattt ttteeaaaeg ttggggaggg
gaaaattcac tgtatcatga aaccctaagg gtttgngtgc acttcctgct ttttagg
                                                                      537
      <210> 638
      <211> 445
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(445)
      <223> n = A, T, C \text{ or } G
      <400> 638
                                                                      60
ccagcagaac acagnagtga tttggtcccg tttgttcccc agtggggtat ctatccttgt
                                                                      120
gcagggcaca agcctacatg gtggctctgg tcatatcatt agaaaataga cagaaatggg
180
agtcaattca tttagactgg tagaaccaga accactgtgt agtacatcca aacggttaaa
                                                                      240
                                                                      300
attccctgga agatgttaca taatcctatc atggtgttta tttatggaaa tctattttaa.
aaattttatg taatactgca cagtctgttt gcatgatgcc ttgtacgtag tagcaactca
                                                                      360
                                                                      420
gtaaatactt tttgaatgaa ctagtatagt attttaatta gctagtcttc gtgtactggt
acaaaagaac agtgtcatct tacag
                                                                      445
      <210> 639
      <211> 584
      <212> DNA
      <213> Homo sapien
      <400> 639
                                                                      60
gcttgagtat tctatagtgt cacctaaata gcttggcgta atcatggtca tagctgtttc
ctgtgtgaaa ttgttatccg ctcacaattc cacacaacat acgagccgga agcataaagt
                                                                      120
                                                                      180
gtaaagcctg gggtgcctaa tgagtgagct aactcacatt aattgcgttg cgctcactgc
                                                                      240
ccgctttcca gtcgggaaac ctgtcgtgcc agctgcatta atgaatcggc caacgcgcgg
                                                                      300
ggagaggegg tttgcgtatt gggcgctctt ccgcttcctc gctcactgac tcgctgcgct
                                                                      360
cggtcgttcg gctgcggcga gcggtatcag ctcactcaaa ggcggtaata cggttatcca
cagaatcagg ggataacgca ggaaagaaca tgtgagcaaa aggccagcaa aaggccagga
                                                                      420
                                                                      480
accgtaaaaa ggccgcgttg ctggcgtttt tccataggct ccgccccct gacgagcatc
                                                                      540
acaaaaatcg acgctcaagt caagaggtgg cgaaacccga caggactata aagataccag
gcgtttcccc ctggaagctc cctcgtgcgc tctcctgttc cgac
                                                                      584
      <210> 640
      <211> 404
      <212> DNA
      <213> Homo sapien
```

```
<400> 640
ccataggaac gcactcaggc aggtggtttg ttctggatgc agaaaccaga gatctagttt
                                                                         60
ctatccacac agacgggaat gaacagctct ctgtgatgcg ctactcaata gatggtacct
                                                                         120
tectggetgt aggateteat gacaacttta tttaceteta tgtagtetet gaaaatggaa
                                                                         180
gaaaatatag gagatatgga aggtgcactg gacattccag ctacatcaca caccttgact
                                                                         240
ggtccccaga caacaagtat ataatgtcta actcgggaga ctatgaaata ttgtactggg
                                                                         300
acattccaaa tggctgcaaa ctaatcagga atcgatcgga ttgtaaggac attgattgga
                                                                         360
cgacatatac ctgtgtgcta ggatttcaag tatttggtgt ctgg
                                                                         404
      <210> 641
      <211> 138
       <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(138)
      <223> n = A,T,C \text{ or } G
      <400> 641
ctgtgacagg aacattacct gaagtgcagg gtggttacct gcacaaagtc ccatttccaa
                                                                         60
aaatttctgt gtaattcacc agaaattttg gatggaataa ttagaaaaaa aaaaagaggt
                                                                        120
taaaacntgt aactcaaa
                                                                        138
      <210> 642
      <211> 381
      <21.2> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(381)
      <223> n = A, T, C \text{ or } G
      <400> 642
ctgtaggtgg aatttttacc cagaaaagat aggccctaga agcctcattt cttttctcca
                                                                         60
tggaaaagga cagccctctg ctgcagcgtt caacttgtgt gtttactqac aqagtgaact
                                                                        120
acagaaatag cttttcttcc taaaggggat tgttctacat tttgaagtta tttttaata
                                                                        180
aaattgaatt atgttgtgta ttgtgcttcc taataggaaa tgcattattg gactgttttt
                                                                        240
gtaacatcct gtttattgca aatagctagt atcgttcaaa aactgtataa aatacttttg
                                                                        300
tacatattag caatgictaa titgiataca citcagitaa atticcciaa aacitqaaag
                                                                        360
gggaccttgt anaaattaaa a
                                                                        381
      <210> 643
      <211> 403
      <212> DNA
      <213> Homo sapien
      <400> 643
ccttcctaaa aaatagtggt gagctggagg ctacttccgc cttcttagcg tctggtcaga
                                                                         60
gagctgatgg atatcccatt tggtcccgac aagatgacat agatttgcaa aaagatgatg
                                                                        120
aggataccag agaggcattg gtcaaaaaat ttggtgctca gaatgtagct cggaggattg
                                                                        180
aatttcgaaa gaaataattg gcaagataat gagaaaagaa aaaagtcatg gtaggtgagg
                                                                        240
tggttaaaaa aaattgtgac caatgaactt tagagagttc ttgcattgga actggcactt
                                                                        300
```

```
attttctgac catcgctgct gttgctctgt gagtcctaga tttttgtagc caagcagagt
                                                                       360
                                                                       403
tgtagagggg gataaaaaga aaagaaattg gatgtattta cag
      <210> 644
      <211> 688
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(688)
      <223> n = A,T,C or G
      <400> 644
cctatttatt tgttttggcc ctggatcttt cctaatcaca attatatttc tttatttttg
                                                                        60
cctttgagca gtttcattta tctttgtggg cagggaagat taaatatgaa attcagtcca
                                                                       120
                                                                       180
gtcattttgc tactggttag ctttagtttg aggcaagtaa aaatttttga ttaaaattag
tttcttaaaa ttatgccctt gctttaccaa ataatcaaat tggctaaaaa ataagggtat
                                                                       240
gtaactttgc attttgaaga acaaaccaat aatttttcat gagccctact cgatcttctt
                                                                       300
taaagaagac cttcctaaga gacaattagg gatgagtttg attaatggga aatagctcta
                                                                       360
                                                                       420
gqttaqatta ttttaaattc catacaccaa gtgatttaac cacagtggca gtggcagctt
                                                                       480
ctgaaccgtc aagtatgaac atcacttaaa aattaaaaga tgcttaataa taaactctta
attttcatta agccaatctg taattcagaa gaaaagcata tgtctgccat gggactattg
                                                                       540
cagtgcgtct ccatcagtgt taacacagga gagatatgtt attttatgtg tatgtcttag
                                                                       600
                                                                       660
tttgggatat gtggtagtaa gaacatgtca agagtgcttt tcttcaaacc tgncagctca
actgangaaa gacaggtact tccattgc
                                                                       688
      <210> 645
      <211> 484
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(484)
      <223> n = A, T, C or G
      <400> 645
ccaaatgtgt ctccagccca cacttccagg tggcagagcg agctctctat tactggaata
                                                                        60
atgaatacat catgagttta atcagtgaca acgcagcgaa gattctgccc atcatgtttc
                                                                       120
                                                                       180
cttccttgta ccgcaactca aagacccatt ggaacaagac aatacatggc ttgatataca
                                                                       240
acqccctgaa gctcttcatg gagatgaacc aaaagctatt tgatgactgt acacaacagt
                                                                       300
tcaaaqcaqa qaaactaaaa qaqaaqctaa aaatqaaaqa acqqqaaqaa gcatgggtta
aaatagaaaa totagocaaa gocaatoooo aggtactaaa aaagagaata acatgaaaac
                                                                       360
gcccagggtt acttgaatgt ttttataaga taggaatata tgtcttcacc atgggggggg
                                                                       420
                                                                       480
gtctcggatt tcactaacgt tgtatatgaa aatgggtgcn ataaaaagta cttttaaact
ttgt
                                                                       484
      <210> 646
      <211> 447
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
```

```
<222> (1)...(447)
      <223> n = A, T, C \text{ or } G
      <400> 646
gggtcgcgtt gaacaacttg gttcaagatg gtgggggcat ttttagagcg gcaataattg
                                                                    60
aaaaaaaagg cgaactctgc cttggagagg tagatgataa gaaataaaaa ggtgtttata
                                                                   120
actattttgt attataaagt gggccttaga gataggaaga agaatgatgg attccttttg
                                                                   180
gatcaatcag aaaggaaaca cgaaagaaaa gtcaggaagg tagagagaga aaaagggagg
                                                                   240
gaaggagaaa gaatgggaat aaaataagga ggtaagagat actatttttg ctgagcaacc
                                                                   300
360
420
tgtgtgtttg taaaatgtgt atgtccc
                                                                   447
      <210> 647
      <211> 388
      <212> DNA
      <213> Homo sapien
      <400> 647
gaaggtgata taaaatgact gtcatcattt ggagtgtgca gtacagttac ttcatgttcc
                                                                    60
teaggtttag aacaatttee eetgeaagtt eteacacaga taggeagaaa teataactaa
                                                                   120
ttttggttaa tcactatggc agccgttgaa gaatttaaga gaacctgcca gtaagatttg
                                                                   180
gaataagatt ctatattatt gcatccacag aaaagaatgt actgatatac tataaactct
                                                                   240
aggagaaaac ttaattgaaa tagtgttatt aagtgttgaa agtaccataa aaatataagg
                                                                   300
gaaaataagc tttcctagaa tttttcagtg ttctagtttt taaacagtga tgtttttat
                                                                   360
taacctattt catccattca aagacagg
                                                                   388 .
     <210> 648
      <211> 632
     <212> DNA
     <213> Homo sapien
     <220>
     <221> misc_feature
     <222> (1)...(632)
     <223> n = A, T, C \text{ or } G
     <400> 648
cctggctggg cntttgacct gcgnttttaa atnactcaca gagggtggga caggaggaag
                                                                    60
agtgaaggaa aaggtcaaac ctgttttaag ggcaacctgc ctttgttctg aattggtctt
                                                                   120
aagaacatta ccagctccag gtttaaattg ttcagtttca tgcagttcca atagctgatc
                                                                   180
attgttgaga tgaggacaaa atcctttgtc ctcactagtt tgctttacat ttttgaaaaq
                                                                   240
tattattttt gtccaagtgc ttatcaacta aaccttgtgt taggtaagaa tggaatttat
                                                                   300
taagtgaatc agtgtgaccc ttcttgtcat aagattatct taaagctgaa gccaaaatat
                                                                   360
gcttcaaaag aagaggactt tattgttcat tgtagttcat acattcaaag catctgaact
                                                                   420
gtagtttcta tagcaagcca attacatcca taagtggaga aggaaataga tagatgtcaa
                                                                   480
agnatgattg gtggagggag caaggttgaa gataatctgg ggttgaaatt ttctaqttnt
                                                                   540
cattccgtac atttttagtt agacatcaga tttgaaatat taatgttacc tcctcaatgg
                                                                   600
ggtggtatca gacctgcccg ggcggncgnn tc
                                                                   632
     <210> 649
     <211> 300
     <212> DNA
     <213> Homo sapien
```

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```
<220>
      <221> misc_feature
      <222> (1)...(300)
      <223> n = A, T, C \text{ or } G
      <400> 649
                                                                         60
nggtgaagat agaanaaata taagcgaaat tggataaaat agcactgaaa aaatgaggaa
                                                                        120
attattggta accaatttat tttaaaagcc catcaattta atttctggtg gtgcagaagt
tagaaggtaa agcttgagaa gatgagggtg tttacgtaga ccagaaccaa tttagaagaa
                                                                        180
tacttgaagc tagaagggga agttggttaa aaatcacatc aaaaagctac taaaaggact
                                                                        240
                                                                        300
ggtgtaattt aaaaaaaact aaggcagaag gctttggaag agttagaaga atttggaagg
      <210> 650
      <211> 498
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(498)
      <223> n = A, T, C \text{ or } G
      <400> 650
                                                                        60
ngtnctgnta aacagaaggg tacaangccc ttctggcttt aagcagtcat aggaatgtga
cagacattee tettagggag egecteetee tagggtttee teatetgtet cacactgagt
                                                                        120
                                                                        180
ggatgtaatg ctattttaat cctgctgtgg cccccaatac tagtacttgt ccataccttc
                                                                        240
ttgcattttt agcgtctgct ctgtggggtt gttaggccct ggcactccca ggaactagtg
ctaaagctgc atctntctct cccctctagg gatcgataaa gtttcactgc agaaagtctc
                                                                        300
cactgcggta tgctgacatc tgccctgaac cttcacccta cagcattaca ggctttaatc
                                                                        360
agattetget ggaaagacae aggetgatee aegtgacete ttetgeette aetgggetgg
                                                                        420
ggtgatcctt ggtgcctttg tttccacaag gccttttcct gccccctgcc ttgccaaaga
                                                                        480
                                                                        498
catttaatca gcacacag
      <210> 651
      <211> 654
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(654)
      <223> n = A, T, C \text{ or } G
      <400> 651
ctgagggtcc ccaggtttct aaagctctca ggacgagaaa gtaggtccca agataaggag
                                                                         60
                                                                        120
cctaaagggc ttttttcttt ctgtgtattc cttcttggcc tccaacatgg gtacagtcac
                                                                        180
aagagcatgt aacagagaag aaggactana cctaccattt tctggataaa gaattggaaa
gaggatccac aggtaaccaa aaagtaccag ggaaatggca gagaaggaaa acctcaggag
                                                                        240
                                                                        300
accaacctca taagtggtat ttattagngc ctgggctcaa atccaaattg tacatgaata
tgtctggtcc tagatagggt accgaagact ttgaaagtga attttggtat atcattgccc
                                                                        360
                                                                        420
agattccaga ctggntattg tgtgacacaa catacaggat atatctgaat agtgctcaga
agagtttgaa aatgcaaatg atattaaaat aaagatgaaa aagagaaagc tggtcagaac
                                                                        480
                                                                        540
ttgtggacat aaccettetg gatetgtnge etgattaaaa aatagttgat attetegaat
gaattaaaac aagatttaga gactgagcat ggtagctnat tcttgtaatc caacnctttg
                                                                        600
ggagggcaag gcaanagaat tgcttgcggc caggagtttt gagaccagct tggg
                                                                        654
```

```
<210> 652
      <211> 293
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(293)
      <223> n = A,T,C or G
      <400> 652
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                                                                        60
cattttcact gtgccttcac atacatctaa tggaaatgaa cagcaccctt catccatcca
                                                                       120
cggaagcgat taagaaaagg gtgggatgga aaaattaacc caacaatatt agatcaatac
                                                                       180
gtagtattta agngtccata atgtgccagg ctgaagatgc acgggaaaac cacactagcc
                                                                       240
ggtctgtcaa gggcttgaga ataccataaa caagaaaaca gacgaaccaa ttt
                                                                       293
      <210> 653
      <211> 294
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(294)
      <223> n = A, T, C or G
      <400> 653
ngtccaccac tgcagcccta catacagttg aaaaaaaatt ccattctgtt aacatttgtt
                                                                        60
ttataagttt tcacgcaata cacaaaaaac ccctctgcac ttcttgtaaa gaacaaaaaa
                                                                       120
gatacacaac agttaagcgt aaagatcaca ggcaatagca ttcaaacatg gatgtgggta
                                                                       180
gagaaaggag tacctggcat gagtacctgc ttagtttgac tgaatccttg atttttaatt
                                                                       240
tggcttttca tgggccgctc acaacaccaa cgctgtgtga ggtatggtag tcag
                                                                       294
      <210> 654
      <211> 250
      <212> DNA
      <213> Homo sapien
      <400> 654
ctgtccttga acaagtatca atgtgtttat gaaaggaaga tctaaatcag acaggagttg
                                                                        60
gtctacatag tagtaatcca ttgttggaat ggaacccttg ctatagtagt gacaaagtga
                                                                       120
aaggaaattt aggaggcata ggccatttca ggcagcataa gtaatctcct gtcctttggc
                                                                       180
agaagctcct ttagattggg atagattcca aataaagaat ctagaaatag gagaagattt
                                                                       240
aattatgagg
                                                                       250
      <210> 655
      <211> 494
      <212> DNA
      <213> Homo sapien
      <400> 655
ccattataat tttataacac cattaccctt taaattctac cgattataag cagcgtaaaa
                                                                        60
gtaactatat aaagcaaaca tcgcaaagga actctgcagg agctcttaat tcctttatgt
                                                                       120
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```
agctatcata aaattcactt tcctgaagac atttactctc attcacttcc aaactccaaa
                                                                       180
cctttttctg gtagcaccac ttttgttttt aatagaaaga tgagttcata tctgtacatc
                                                                       240
tctccaaagc tctaaggaat gagaaaagga tcctagtata ttgaaattac tgatgtttaa
                                                                       300
tacctctqcc ttttcactaa aagccattta atattttaa agtcaaaact tgacatacag
                                                                       360
gtatttataa ggaatctcca tgactctgaa ggaatgaaat tgatgtaggt agctttggct
                                                                       420
atgtaaagac atagtagagg acaattactt aaagaagagt tttcttttga ggatttgtag
                                                                       480
atttgactaa gcag
                                                                       494
      <210> 656
      <211> 477
      <212> DNA
      <213> Homo sapien
      <400> 656
cgcgttactg tacatattgc tagcaggaga caactggaaa tactaaacaa atactggaat
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tcacattaca gacagacgaa accaacatgg atgccacaca taacttcctt tgtagtttca
                                                                       120
caqaqqqcct atttqtqqtt qctcaqqtqq qqtcatacat tgcttqcaqa aatggcctga
                                                                       180
tcatagctct atgaaacaat gaattcggaa tgaaatctta ccatgacacc tctctgtagg
                                                                       240
                                                                       300
aaagaaatgt tgcttcacgt gtgctaagtt gagataataa tatttcacat atttatatac
agagaatcac tctcaaattt aacccaagat aagcaatagg atttgggggt gacttgtaca
                                                                       360
catttctaac aacacttttc tttttctag aggtcactct caaacactga tatatcacta
                                                                       420
                                                                       477
tagtttgagt gtagggattc agtaatcaaa ggttgttatt gcaaaagagc caggcag
      <210> 657
      <211> 576
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(576)
      <223> n = A, T, C or G
      <400> 657 ·
cctctacctg tanatcacta tttttctaaa gacaatttgg tgttttgaag ataaatgtca
                                                                        60
ttagtctatg ataatagcat cataggacaa ttagccattt tagacttgac catattttct .
ctttttagca tatagccatc ttgatattta ggtgggagac tactccaatg gagcaacagt
                                                                      180
ttcattttac atgattggat ttagaaattt acaaatttta aactcataag aattctaaat
                                                                       240
                                                                       300
aatttqaaaa tqqaaacatt tqacccacag tctagcagca taaatacatt tataaaatac
ttcattgttg atcttaggtc attgatttaa aacagaattt ggtgactatg ggcaggtgga
                                                                       360
                                                                       420
gggggccagt gaggaaggta taaaagagaa atctttatga attgtgttca gattgatttt
gtataaacat aatattca tggttgtatc tcttatttat aatacccaac taacatgaag
                                                                       480
gtggtccaag ggaaggatca atattttaaa taacatattt gcttaaaata tcatacagtg
                                                                       540
                                                                       576
gctgcttcat aaaaaatctt ataaactttt attacc
      <210> 658
      <211> 344
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(344)
      <223> n = A, T, C or G
```

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<400> 658
cctgaaaaga aagntgctct tatggactct tgcatgttaa gactatgtct tcacatcatg
                                                                        60
gtgcaaatca catgtaccca atgactccgg ctttgacaca acaccttacc atcatcatgc
                                                                       120
catgatggct tccacaaagc attaaacctg gtaaccagag attactggtg gctccagcgt
                                                                       180
tgttagatgt tcatqaaatg tgaccacctc tcaatcacct ttgagggcta aagagtagca
                                                                       240
catcaaaagg actccaaaat cccataccca actcttaaga gatttgtcct ggtacttcag
                                                                       300
aaagaatttt catgagtgtt cttaattggc tggaaaagca ccag
                                                                       344
      <210> 659
      <211> 230
      <212> DNA
      <213> Homo sapien
      <400> 659
ctgctttccc tgctaaacag ttccagaqca aaaqcaqcaa aaaqaaaata tqqqaqqqat
                                                                        60
atgggcaacg tatactcgaa cgtacgcaga gaagagagta cggttagctc taatatttct
                                                                       120
cattgaactt ggtggtatgt gccttccctg catataaggc catagtgctt ttttgggagc
                                                                       180
gctagaatat ccatccactt gacagtgacc acaaaatagg ctgtttccag
                                                                       230
      <210> 660
      <211> 80
      <212> DNA
      <213> Homo sapien
      <400> 660
ctggtccttg ttaaactcga tcaccacttt ggagagatcg actggaggct cctgggtgtt
                                                                        60
ctgagggcc tgggggacag
                                                                        80
      <210> 661
      <211> 535
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(535)
      <223> n = A, T, C \text{ or } G
      <400> 661
ctgaaccata tctgattaac tctttggtct ctgttattgg aacaaaaccg acgctatgcc
                                                                        60
tgcagccgcc agactgcaac caaaaacaca gtttggggtc agaagacatt aaaaatcaca
                                                                       120
ataaaatagg atgaatgttc taagtcacgc aactgaatca aggcaccttt tttttcaaa
                                                                       180
agcaaaaagt tgtttaacaa tattccagaa tagtagatac ttcaaaaacc agattacagt
                                                                       240
atatatcatt ttgctgcaca ttttagtcta ttttctgtat acatagtcac acattcttta
                                                                       300
ccctctccca acttatacat gctttatccc cccagtcatg tgctatgtag gtataaaaaa
                                                                       360
ataaagttgt atctaaacaa gtgatttaaa aaaaaaaact aacqaatqcc ncnatnataa
                                                                       420
cnctgaactt gtttccctnt tgaaggacat tggaaatgtt accgaggttn ntttacctng
                                                                       480
gccgcaaccn cnctangggc naattccagc ncactggggg ccgttactag gggat
                                                                       535
      <210> 662
      <211> 257
      <212> DNA
      <213> Homo sapien
      <400> 662
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214

60 cctgactaaa qcacatatca cactccctac acttccatgt tttctctccc atgtggaccc totgatgcat atcaagatto aagogootgt tgtagcoott cocacagtoo tcacatttgt 120 atggcttttc tacactgtga actttttctt gcactttaga gaatgaattc tgtacaatgt 180 tcttcccatg ctgctcacat ttgagaggtg tttctctgct gtggcgtctc tgatgggtca 240 257 gacgagttga ggaccag <210> 663 <211> 516 <212> DNA <213> Homo sapien <220> <221> misc feature <222> (1) ... (516) <223> n = A, T, C or G<400> 663 60 ccaattatag gtattttatt ttttaaagat tagagngttc ttgaagctct ttctatttct ttgtcaatga actaaacatt ggcaaatatg tagggtttcc cacataagaa cattattaac 120 atcaaaatag aaagctggtg gtagaaataa tgattgggaa cacagagtct ctactcagcg 180 240 ttctacttct gccataccat aactttgtga tctcacgaaa tatctctcca tgttctcatc 300 cctatgtata gttctgtcat ttttcaataa gagctttttg cttaattatg aagtactagt tactataacc attattttga gcttcatgta aatcaagaac acatggactc cacttgcaaa 360 acattgaaaa tgtagttagg gattgggggc aaaaagcaac attttaaaat gtgtaaagac 420 aatgagtaag caacaaagtg tccaattttt taggcgaaag ttgcatatgt caggaaaagg 480 516 caggattaag taatagagaa tttgaatgat aactgg <210> 664 <211> 212 <212> DNA <213> Homo sapien <400> 664 60 gtccgaggag gttagttgtg gcaataaaaa tgattaagga tactagtata agagatcagg 120 ttcgtccttt agtgttgtgt atggctatca tttgttttga ggttagtttg attagtcatt gttgggtggt aattagtcgg ttgttgatga gatatttgga ggtggggatc aatagagggg 180 212 gaaatagaat gatcagtact gcggcgggta gg <210> 665 <211> 408 <212> DNA <213> Homo sapien <220> <221> misc feature <222> (1)...(408) <223> n = A, T, C or G<400> 665 atccagggt ncccggtngc tgcngggaaa cctccagcct tgttcttcaa accactcagc 60 tcatgtgttt tgcgctgact agtactgaat aatacaacca ctcttattta atgttagtat 120 180 tatttatttg acaactcagt gtctaacagc ttgatatgca ggtccttgca tcctacattt ctttaggaag ttacccattt gtaactttaa aaacaggaaa aatatcagtt ggcaaatgca 240 300 atctttttt tttttaagct aaaggggggn naacngnaan naaaatnttt ntgangtngg 360 gtctataagc accettgang ggatntgtta aaagngneat naanggggga ttetentttn

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gcaaaaaaat ntaannatca atttatanan ctttattttt nactttnt
                                                                        408
      <210> 666
      <211> 635
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (635)
      \langle 223 \rangle n = A,T,C or G
      <400> 666
                                                                        60
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cacctgaaga aatcgaaagg atggttaatg atgctgagaa gtttgctgag gaagacaaaa
                                                                        120
agctcaagga gcgcattgat actagaaatg agttggaaag ctatgcctat tctctaaaga
                                                                        180
atcagattgg agataaagaa aagctgggag gtaaaccttc ctctgaagat aaggagacca
                                                                        240
                                                                        300
tggaaaaagc tgtagaagaa aagattgaat ggctggaaag ccaccaagat gctgacattg
aagacttcaa agctaagaag aaggaactgg aagaaattgt tcaaccaatt atcagcaaac
                                                                        360
tctatggaag tgcaggccct cccccaactg gtgaagagga tacagcagaa aaagatgagt
                                                                        420
tgtagacact gatctgctag tgctgtaata ttgtaaatac tggactcagg aacttttgtt
                                                                       480
aggaaaaaat tgaaagaact tanctctcga atgtcattgg aatcttcacc tcacagtggn
                                                                        540
gttgaaactg ctatagccta agenggetgt ttactgnttt neattagcag gtgeteacea
                                                                       600
tgtctttggg gtgggngggg ggagaaagaa agaan
                                                                       635
      <210> 667
      <211> 388
      <212> DNA
      <213> Homo sapien
      <400> 667
gaaggtgata taaaatgact gtcatcattt ggagtgtgca gtacagttac ttcatgttcc
                                                                        ·60
tcaggtttag aacaatttcc cctgtaagtt ctcacacaga taggcagaaa tcataactaa
                                                                       120
ttttggttaa tcactatggc agccgttgaa gaatttaaga gaacctgcca gtaagatttg
                                                                       180
gaataagatt ctatattatt gcatccacag aaaagaatgt actgatatac tataaactct
                                                                       240
aggagaaaac ttaattgaaa tagtgttatt aagtgttgaa agtaccataa aaatataagg
                                                                       300
gaaaataagc tttcctagaa tttttcagtg ttctagtttt taaacagtga tgtttttat
                                                                       360
taacctattt catccattca aagacagg
                                                                       388
      <210> 668
      <211> 498
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(498)
      <223> n = A,T,C or G
      <400> 668
tgatcttaac aaaattcgta gcagtggaac cttgaaatgc atgtggctag atttatgcta
                                                                        60
aaatgattot cagttagcat tttagtaaca cttcaaaggt ttttttttgt ttgttttcta
                                                                       120
gacttaataa aagcttagga ttaattagaa gaagcaatct agttaaattt cccatttgta
                                                                       180
ttttattttc ttgaatactt ttttcatagt tattcgttta aaaagattta aaaatcattg
                                                                       240
                                                                       300
cactttggtc agaaaaataa taaatatatc ttatgaatgt ttgattccct tccttgctat
```

ttttattcag tagatttttg aaaaggctat agagtccaaa gaggaatttg ttttcgcctt gttnttaata tgagattt	ggaatgttct	tttacaccaa	ttcttccttt	aaaaatntct	360 420 480 498
<210> 669 <211> 622 <212> DNA <213> Homo sapie	en .		,		
<400> 669					
ccttagccaa agaatgcagt	ggagccttcc	cccttcaact	gcattgtgaa	tgaataccaa	60
ttaacagcat aaaaattaat					120
gatgtcccta tcctgttgta					180
tataaagtct tggtaaaaca					240
gaggaaaagt gaaaaggact					300
cctgtaataa gctgagtgca					360
aagcactgca gagaacaggg					420
ctttgttcaa ggtaaccttg					480 540
tagctctaca ctgcatttga aatgtgcttt ttacactgca					600
ttatgttcat ttgctcacag		adddccggcc	ageaaaceee	cagegageae	622
<210> 670 <211> 477 <212> DNA <213> Homo sapie	en				
. <400> 670					
ttgggccctc tagatgcatg	ctraaacaac	caccaatata	atggatatct	gcagaattcg	60
cccttgccgc ccgggcaggt					120
gatatctaca aggctaataa					180
ccagtagagg agaaaataga					240
atagaaaaaa atgaacaaat					. 300
gaagaagatc ttcggaaaga					360
gcctatttga aaaggttagt					420
ggggaaaggg ccaccaggct	ttttgagaaa	cctcttgatt	ctcagtctat	ttatcag	477
<210> 671 <211> 127 <212> DNA <213> Homo sapie	en				
400- 671					
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tgtgtgtgtg cgtgtatttc acctgag					120 127
-210, 672					
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<211> 400 <212> DNA				•	
<213> Homo sapie	en		•		
*					
<400> 672					
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ggaaaagcaa ttcaagctgg tcacacagtg taatgcaaaa tatgtggaat gtttcagtgc
                                                                        120
tcagaaagag tgtaacaaag aaaagaacag aaactcttca gttgtgccat ctgagcgtgc
                                                                        180
tcgagtgggt cttgcaccat tgcctggaat gaaaggaaca gattacatta atqcttctta
                                                                        240
tatcatgggc tattatagga gcaatgaatt tattataact cagcatcctc tgccacatac
                                                                        300
tacgaaagat ttctggcgaa tgatttggga tcataacgca cagatcattg tcatgctgcc
                                                                        360
agacaaccag agcttggcag aagatgagtt tgtgtactgg
                                                                        400
      <210> 673
      <211> 600
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(600)
      <223> n = A, T, C \text{ or } G
      <400> 673
ctggcgttgc tcattagtga atgtatgaca gcaggatgtg aggggatgcc caggagtcag
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tgttagcatt gtcatctgag atcactgcta ttaatatcat ccattaattt attagtgagc
                                                                        120
ttcactatat gcagactggg agataaggag aaaatctgtc acattctctc tagctaatca
                                                                        180
gatcagctac caattaatga gattctgaat gaaatatcaa tatgtgtttt tctaatttgg
                                                                        240
acctaggaca gagctgttgc ttgtcataga gaaaaacaat aatgcttaaa cataqcacat
                                                                        300
tataattaaa gcaggtttct cacatacttt tcattttatc ctttggataa ttttgtgagg
                                                                        360
aacgcaggac accaacttcc ctttcataga tacaatcccc atgctattga tgaaagtgtt
                                                                        420
tttgaatgaa gccatacaac aaataactga tcaaagtggc attacaccaa aatttcttag
                                                                        480
taggactcct gcatagaatg tttagataga cgtgaaaagt ttgttcanga ggaccagcaa
                                                                        540
gagagaaact gggttctttg ggagggtttc ggtgctacat ttataccctn catcagagtn
                                                                        600
      <210> 674
      <211> 140
      <212> DNA
      <213> Homo sapien
      <400> 674
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                                                                        60
gattaaggat actagtataa gagatcaggt tcgtccttta gtgttgtgta tggctatcat
                                                                        120
ttgttttgag gttagtttga
                                                                        140
      <210> 675
      <211> 245
      <212> DNA
      <213> Homo sapien
      <400> 675
gttgggtggt tggtgtaaat gagtgaggca ggagtccgag gaggttagtt gtggcaataa
                                                                        60
aaatgattaa ggatactagt ataagagatc aggttcgtcc tttagtgttg tgtatggcta
                                                                       120
tcatttgttt tgaggttagt ttgattagtc attgttgggt ggtaattagt cggttgttga
                                                                       180
tgagatattt ggaggtgggg atcaatagag ggggaaatag aatgatcagt actgcgqcgg
                                                                       240
gtagg
                                                                       245
      <210> 676
      <211> 621
      <212> DNA
      <213> Homo sapien
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<220>
      <221> misc feature
      <222> (1)...(621)
      <223> n = A, T, C \text{ or } G
      <400> 676
ctgtccccag ggnaaatagt ngaattcaac taagatctgt taataagatg tcagaataac
                                                                          60
taataatttt attaggaaaa aatcatgttt taaatttcaa aatgacactt atttgtcaag
                                                                        120
taatatgatc ttggaaaatt ttaaagaaaa ataatcctac ttataaacta ctttttata
                                                                        180
attqttttca qaaaaaaaqt ttacaqtctt aaggaaaata ttcaqgtcta tcatatggtt
                                                                        240
                                                                        300
tgacagattt tttaaaagtt atttttggta aggtcttctt ttagaaaaaa attaatctca
agggtttttt gtaccactat aatctctaat acttactcag aattactgtg tatttactta
                                                                        360
atticttatt atgigccita tiatgigcit aagatacaat aggitagagi tiaatciaaa
                                                                        420
tatcttgaaa gctatattgt gggcttggta agcattttgt tttttctttc tctgttttgg
                                                                        480
                                                                        540
taaggattta aaattttttt cattgcaatt ttaagtggtt ttcaataagt aatagttttt
atcaaatttt tggtgcttgg tgcagagacg gcgtggggaa gggtgaatgg ttttgggaat
                                                                        600
aattcagtgc acacctgggg g
                                                                        621
      <210> 677
      <211> 210
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
    <222> (1)...(210)
      <223> n = A, T, C \text{ or } G
      <400> 677
tttacataan atattatcag catttaccat ctcacttcta ggaatactag tatatcgctc
                                                                         60
acacctcata tcctccctac tatgcctaga aggaataata ctatcactgt tcattatagc
                                                                       · 120
tactctcata accctcaaca cccactccct cttagccaat attgtgccta ttgccatact
                                                                        180
                                                                        210
agtctttgcc gcctgcgaag cagcggtagg
      <210> 678
      <211> 383
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(383)
      <223> n = A, T, C \text{ or } G
      <400> 678
                                                                         60
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agggttaggg tggttatagt agtgtncatg gttattagga aaatgagtag atatttgann
                                                                        120
aactgattaa tgtttgggnn tgagtttnta tatcacagcc anaattntat gatgnaccat
                                                                        180
gtancgaaca atgctacagg gatgaatatt atggagaagt antctanttt gaagcttagg
                                                                        240
gagagetggg ttgtttgggt tgnggetean tgteagttee anataataae ttettggtet
                                                                        300
aggcacatga atattgttgt ggggaanaga ctgataataa aggtggatgc gacaatggat
                                                                        360
                                                                        383
tttacataat gggggtatna gtt
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219

<211> 371 <212> DNA <213> Homo sapien <400> 679 aaaatgaaaa tattgacaag agtttcagat agaaaatgaa aaacaagcta agacaagtat 60 tggagaagta tagaagatag aaaaatataa agccaaaaat tggataaaat agcactgaaa 120 aaatgaggaa attattggta accaatttat tttaaaagcc catcaattta atttctggtg 180 gtgCagaagt tagaaggtaa agcttgagaa gatgagggtg tttacgtaga ccagaaccaa 240 tttagaagaa tacttgaagc tagaagggga agttggttaa aaatcacatc aaaaagctac 300 taaaaggact ggtgtaattt aaaaaaaact aaggcagaag gcttttggaa gagttagaag 360 aatttggaag g 371 <210> 680 <211> 176 <212> DNA <213> Homo sapien <400> 680 cctaggattg tgggggcaat gaatgaagcg aacagatttt cgttcatttt ggttctcagg 60 gtttgttata attttttatt tttatgggct ttggtgaggg aggtaagtgg tagtttgtgt 120 ttaatatttt tagttgggtg atgaggaata gtgtaaggag tatgggggta attatg 176 <210> 681 <211> 152 <212> DNA <21.3> Homo sapien <400> 681 ctggagatgg atatgagact agtcaagatg tgaatgctaa ttggagagaa atataatttt .60 aggaagatge acattgatgt ggggttttga tgtgtetgat tttgaetaet caagetetgt 120 ttacagaaga aaattgaatg gcgagggtgt gg 152 <210> 682 <211> 141 <212> DNA <213> Homo sapien <400> 682 ccagtgcttg cttgccgtgg tttagtgatt gggtgttaga aataaaaact caggtctatt 60 120 gaactttgtt ggggtggggg g 141 <210> 683 <211> 308 <212> DNA <213> Homo sapien <400> 683 ccagcaatgg tacagagtga gggtgttctg ctaatgactt cagagaagta tttaagaaaa 60 acatagaaaa acgtgtgcgg agtttgccag aaatagatgg cttgagcaaa gagacagtgt 120 tgagctcatg gatagccaaa tatgatgcca tttacagagg tgaagaggac ttgtgcaaac 180 agccaaatag aatggcccta agtgcagtgt ctgaacttat tctgagcaag gaacaactct 240 atgaaatgtt tcagcagatt ctgggtatca aaaaactaga acaccagctc ctttataatg 300 catgtcag 308

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<210> 684
      <211> 277
      <212> DNA
      <213> Homo sapien
      <400> 684
tggtattagg attaggatgt gtgaagtata gtacggatga gaaggttggg gaacagctaa
                                                                         60
                                                                         120
ataggttgtt qttgatttgg ttaaaaaata gtagggggat gatgctaata attaggctgt
qqqtqqttqt qttqattcaa attatgtqtt ttttggagag tcatgtcagt ggtagtaata
                                                                        180
taattqttqq qacqattaqt tttaqcattq qagtaqqttt aggttatgta cgtagtctag
                                                                         240
                                                                         277
gccatatgtg ttggagattg agactagtag ggctagg
      <210> 685
      <211> 457
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(457)
      \langle 223 \rangle n = A.T.C or G
      <400> 685
ctgtggcgtn ccctacttct cccaaacctc gcaactccct cccaggacag tcagtgccaa
                                                                         60
aqaaacaqqt cqctqaaaac taaaatgtcc acatccctaa ctggcaaccc acatcaaccc
                                                                         120
caaaaqqttq aaqaatcatc taagatattt cagatgctct atgaagaaat tcactttaac
                                                                        180
acttataact qtaaqacttt qcatacatta caacagtgca ttagtgatac aagttgtaaa
                                                                        240
atacgtttcc attcctttgg attttgcata tgatggtttt gcatcagtca ctgcaggtag
                                                                        300
attgagcaag ctttttgtgt ttgtttttt aaacatgcat tcaactagat atgattcaga
                                                                        360
atagattaat actccctttt tatcactaca gttagctaaa aaattgccag gcagtccaca
                                                                        420
                                                                        457
aaacagaatt tgctttaaga ccaacccaca gagtcag
      <210> 686
      <211> 234
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(234)
      <223> n = A, T, C \text{ or } G
      <400> 686
ntggatttat aaaatagttg caatgacaaa agaagtatgt tttgacagta aaaaaaaagac
                                                                         60
                                                                        120
attatggaca aaatatgcaa aatgtgcaaa gaaaaaataa atttgcatta gaaaggtggg
catttgatct ctgagccctg tgccatgtaa cattgccatg ttctttcact gttgtttgaa
                                                                        180
tqttqtaccc caqcccttqa ctctqqactt aaggcaagct atgactggct ttgg
                                                                        234
      <210> 687
      <211> 315
      <212> DNA
      <213> Homo sapien
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<220>

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<221> misc_feature
      <222> (1)...(315)
      <223> n = A.T.C or G
      <400> 687
nngtctgtga aaaactcttt ggatgattct gccaaaaagg tacttctgga aaaatacaaa
                                                                         60
tatgtggaga attttggtct aattgatggt cgcctcacca tctgtacaat ctcctgtttc
                                                                        120
tttgccatag tggctttgat ttgggattat atgcacccct ttccagagtc caaacccgtt
                                                                        180
ttggctttgn gtgtcatatc ctattttgtg atgatgggga ttctgaccat ttatacctca
                                                                        240
tataaggaga agagcatctt tctcgtggcc cacaggaaag atcctacagg aatggatcct
                                                                        300
gatgatattt ggcag
                                                                        315
      <210> 688
      <211> 522
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(522)
      <223> n = A, T, C \text{ or } G
      <400> 688
ctgaattaga ggaggagaaa agaagccatt nnggagtact ttaattgttt agatgtgaga
                                                                         6.0
ggctgaatgt ttgggttaag atgttagttg tcagaatcat gagaaaaggt tttaagcaag
                                                                        120
gggcatttct aattctaaaa ataacaacta ctgttattta ttgaqcacta tctttttqtt
                                                                        180
gggtactgtc taaagtactt gatttatttt ttaaaacctt acaaaaaact tacaaggtag
                                                                        240
gtactgaaag attcagtaat ttgttcaaag tcacacagca aataagcaac agactctgga
                                                                        300
tttgaaccag gcaatcctag agcctgtact gttagtaatt atactttagc acctgtcaag
                                                                        36.0
aattcctgtt gagtgtcaag aagcaancac caagttagga tttaaagcaa acatgattga
                                                                        420
agaatactgt ggtgtggttg acagtagtgc ctaaqtctqt tttcaqagtq aaaaatqaca
                                                                        480
aattagattt taagtatggt ttggagataa tatcaggaca gt
                                                                        522
      <210> 689
      <211> 158
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(158)
      <223> n = A, T, C or G
      <400> 689
tctcaactta ntntnatacc cacacccacc caanaacagg gtttgttagg nattgtttgc
                                                                         60
attaataaat taaagctcca tagggtcttc tcgtcttgct gtgtcatgcc cgcctcttca
                                                                        120
cgggcaggtc aatttcactg gttaaaagta agagacag
                                                                        158
      <210> 690
      <211> 300
      <212> DNA
      <213> Homo sapien
      <220> -
      <221> misc_feature
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<222> (1) ... (300) <223> n = A, T, C or G<400> 690 taqaactcqt atttttaaac ttctattctc tanccttttc cactacatta tgacacaaga 60 ccctgcagaa agtcgtctgg aaaatatcag accatctctt acttgtccca tccaatctta 120 catcgaatta tatgcaccct taaaaagtta tttggagttt taaaaaactc tattagccca 180 aattacctga aataaactcc tggcttgttc ccctaatgtt tataaaaaat tgattgaaaa 240 tattcatttt aaaaatgaag ntcttgaatt tatttaaatt actgtcttgc agtgagttgg 300 <210> 691 <211> 305 <212> DNA <213> Homo sapien <400> 691 60 ctgttcagaa agctcattgg acctggtttt gaaaataaaa caaagttaaa accctgggag qaqttattqt qcaqtqtqqa qtactcaggc tttcttataa agaaaaaaa agttatctgg 120 taccaaagtg tgcaacctac agaccctcag gtactgccct gtgacttctc tgtatgacat 180 cacaaggetg ccaagtgeet gtttttetag aactaggagt tggtgaggtt tggetagtge 240 300 tqaaaccatq cataqqattq gtttactaaa ttaaaacctt attacgtacg tcctccaaaa 305 gacag <210> 692 <211> 582 <212> DNA <213> Homo sapien <400> 692 60 caggaaatgg ataaccattt taactgtatt ttttgcagcc cgtaccttct tgggaataca attgtctaac tttttatttt tggtctggct gttgtggtgt gcaaaactcc gtacattgct 120 180 attttgccac actgcaacac cttacagatg tggaagatgt gaaatttgtc atcaattatg actaccctaa ctcctcagag gattatattc atcgaattgg aagaactgct cgcagtacca 240 300 aaacaggcac agcatacact ttctttacac ctaataacat aaagcaggtg agcgacctta tctctgtgct tcgtgaagct aatcaagcaa ttaatcccaa gttgcttcag ttggtcgaag 360 420 acagaggtgc aggtaaggat gactgatagg aaatgttggt agttacgagt cacatcgttg tctacaaatc catttaaatg gtattggagg gtgagtaaaa ccttgaatgt gaaaacttaa 480 gctgaaaaat tgtaaaaaca tttcacgcct accatgaata gatctgtttc tttctgtcca 540 582 caatgatttg tgtcatagac ataattgatc aatttgcaat tg <210> 693 <211> 275 <212> DNA <213> Homo sapien <400> 693 ccaattgatt tgatggtaag ggagggatcg ttgacctcgt ctgttatgta aaggatgcgt 60 agggatggga gggcgatgag gactaggatg atggcgggca ggatagttca gacggtttct 120 atttcctgag cgtctgagat gttagtatta gttagttttg ttgtgagtgt taggaaaagg 180 gcatacagga ctaggaagca gataaggaaa atgactatga gggcgtgatc atgaaaggtg 240 ataagctctt ctatgatagg ggaagtagcg tcttg 275 <210> 694

<211> 397

<212> DNA

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<213> Homo sapien
       <220>
       <221> misc feature
       <222> (1)...(397)
       <223> n = A, T, C or G
       <400> 694
nggtctgcat ttttattgcg atctgcagat gaactggaaa atctcatttt acaacagaac
                                                                         60
tgagacagac gaccaccata ttcactgagg tctaaatttg cagtttccac taatgacatt
                                                                        120
ttgatttccc aacagagata cttctggtct tactgcacag tcttttaaga gaaatacttc
                                                                        180
cattatgcca cattgtcctt gatccgtaag tgatgtgtta aggtgcttca aaggaactct
                                                                        240
gacctctgaa gtacttgagc tactttagta tgtccagcct attgcttttt gttttagtgt
                                                                        300
gtcaccataa atatcagggg cataaaaggc tatctattct taattcaagg ataaaacaga
                                                                        360
agaagcttgt ggtataaaac aatagttcaa gatccag
                                                                        397
      <210> 695
      <211> 609
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(609)
      <223> n = A, T, C or G
      <400> 695
ctgagcttcc atttgtcagc tagcactgng gtagtcaacc atgcgaatga ggctattttg
                                                                         60
gacctcatga ttgtccagtg cctgggctga taccgnggga aacgaaattt tgtggctgcc
                                                                        120
cacaaaatca tggaaaataa tgatttttta gaaaacctcc actgntttgt tgtgcagcaa
                                                                       180
taaataactg aaacaccaat ccaaaaaact tataaagcta taacaattaa aacagnataa
                                                                        240
taatagtncc gggatacaaa aatggtcaaa ttgaagagga tacaaagcct caaagcagtc
                                                                        300
ctcactcata ananccttgt tgtatcacta aaanggcatt aaaattgaga anaaggaana
                                                                        360
actagtggat taattaataa atgagaagta tccataagga aaaattaaaa ttnnattctt
                                                                        420
gcttcacatt atgaaaaaat acaaacaaca gattgattaa agacttaaat gngatcaaca
                                                                       480 .
aaatgttaaa actgtgataa gaacatttaa gaaaatagtt ctatnaccct gggataaaac
                                                                       540
attttcntcc aaggcattaa agtgttaaat gaaaagactg atncatttat tcattagaat
                                                                       600
ttaaattcn
                                                                       609
      <210> 696
      <211> 300
      <212> DNA
      <213> Homo sapien
      <400> 696
ctgcaaaata agcgtgctaa attaaattgt cttaaggttt ttccacttca ttttgtgact
                                                                        60
ttgtgtggtt cgaatttctc agtattttaa ccagtgtgtt gatgttaaag tcaaaggctg
                                                                       120
cagtatgtct atattcttgc tgtactcatt ggtagtttca gtatatgtaa tgtgagttta
                                                                       180
aatagtgaaa ttgtatctca tattaacatt tcaaatgctc atattgaaaa tggaaaatag
                                                                       240
taaacacggg aattgatttt attctggttg tctataatac ttcattttaa atgtaaatgg
                                                                       300
      <210> 697
      <211> 391
     <212> DNA
      <213> Homo sapien
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<220>
      <221> misc_feature
      <222> (1)...(391)
      <223> n = A, T, C \text{ or } G
      <400> 697
nngtcatgtn tgatgnatct gancaggttg ctccacaggt agctctagga gggctggcaa
                                                                         60
                                                                        120
cttagaggtg gggagcagag aattctctta tccaacatca acatcttggt cagatttgaa
ctcttcaatc tcttgcactc aaagcttgtt aagatagtta agcgtgcata agttaacttc
                                                                        180
                                                                        240
caatttacat actotgotta gaatttgggg gaaaatttag aaatataatt gacaggatta
                                                                        300
ttggaaattt gttataatga atgaaacatt ttgtcatata agattcatat ttacttctta
tacatttgat aaagnaaggc atggttgtgg ttaatctggt ttatttttgn tccacaagtt
                                                                        360
                                                                        391
aaataaatca taaaacttga acaaaaaaaa a
      <210> 698
      <211> 536
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(536)
      <223> n = A, T, C \text{ or } G
      <400> 698
                                                                         60
ctgagcatac agcaataaaa ataacataat ttttatgtgt acaatattta tggaatacgt
tactggaaca gataaataat ttagttaata acatgacaaa gaacagaaat tgtatacact
                                                                        120
atacagcata gtaatagaat aatgaatgat taaagttatt aatattaggt agaaaatgaa
                                                                        180
                                                                        240
gggtatcttt gagagcagaa ctcaaggaag caagcaattt gccttatgag gaaagagtta
cctqtqqata aaqqaqaaac tgaaaaattt acaagtcaag actttttgag caaagacaaa
                                                                        300
                                                                        360
aatatgacta tgagtcacca attcagtaca gtgaaaaaaa agttgaagag atatcttgga
agtaaaccat gttgtggaag agcagggttt tgataatcat gggattattc tgaatgaatt
                                                                        420
                                                                        480
ttaaatgcga taggaatata tgagataatt tcaccagaga ataatatgat catgtttgca
tttcaaaggg gtgtatctgg tgcactgngt agaataaata ggntatgtga gcaagt
                                                                        536
      <210> 699
      <211> 419
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(419)
      \langle 223 \rangle n = A,T,C or G
      <400> 699
                                                                         60
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acacacaaga gttgataact tcctcatgaa ctccttgcct gatctaaact catattatgg
                                                                        120
gttctgactg tttgagtaat catcttcaag gttaaacctc ttggcagtta cccttttcac
                                                                        180
                                                                        240
aaagtgcaca gtgggaatcg agaatcgata gggttaattt tggagcagtg gcttatacca
ttcacctctg tttttttgtg attatttcac agataatgag accttaataa caaataggcg
                                                                        300
                                                                        360
taaaaaaatt ttcacattga aatgatagaa acatttgatg taataaaact tggttggctt
gatattttaa ggaattgaaa cctagcaatc ttattggaga gacaagaatt ggtctccag
                                                                        419
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<210> 700
      <211> 336
      <212> DNA
      <213> Homo sapien
      <400> 700
ccacttattg tccttaaaaa tccatactga tacatggaca gfaagtgtgt tttcagatgg
                                                                         60
agtaccagca ccgaaaatgg gttgagggag gatgggttgt atgtatgttt ctgcccacta
                                                                        120
attttqaqca qccatattat qaattaaatc qtcacaqcca aqtaataacc caaqaatqqt
                                                                        180
atgagtttca tgtgtaatag ctcaaatgga ataagcatga atgctggagt ggaccattat
                                                                        240
cctcaaatat tctatgtcac ttctcattta aagactcttg ttatgaacta ttaqaaactt
                                                                        300
taggcaaaat caaaagtatt tgcggcaaaa taaagg
                                                                        336
      <210> 7.01
      <211> 418
      <212> DNA
      <213> Homo sapien
      <400> 701
ccatgtgatg atgttgacaa cccctgaaga gcctcagtcc attgttccac gtttaagaac
                                                                         60
taggaatacc aggactgatg caattctact gggtcactat cgcttgtcac aagacacaga
                                                                        120
caatcagacc aaagtatttg ctgtaataac taagaaaaaa gaagaaaaac cacttgacta
                                                                        180
taaatacaga tattttcgtc gtgtccctgt acaagaagca gatcagagtt ttcatgtggg
                                                                        240
gctacagcta tgttccagtg gtcaccagag gttcaacaaa ctcatctgga tacatcattc
                                                                        300
ttgtcacatt acttacaaat caactggtga gactgcagtc agtgcttttg agattgacaa
                                                                        360
gatgtacacc cccttgttct tcgccagagt aaggagctac acagctttct cagaaagg
                                                                        418
      <210> 702
      <211> 261
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(261)
      \langle 223 \rangle n = A,T,C or G
      <400> 702
gggcctgttg tgggggtggg ggaagcaggg aggggaacag ctaaataggt tgctgttgat
                                                                         60
ttggttaaaa aatagtaggg ggatgatgct aataattagg ctgngggtgg ttgtgttgat
                                                                        120
tcaaattatg tgttttttgg agagtcatgt cagtggtaga aatataattg ttgggacnat
                                                                        180
tagntttagc attggagtag gtttaggtta tgtacgtagt ctaggccata tgtqttqqan
                                                                        240
attgagacta gtagggctag g
                                                                        261
      <210> 703
      <211> 261
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(261)
      <223> n = A, T, C \text{ or } G
      <400> 703
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60
gggcctgttg tgggggtggg ggaagcaggg aggggaacan ctaaataggt tgctgttgat
ttggttaaaa aatagtaggg ggatgatgct aataattagg ctgngggtgg ttgtgttgat
                                                                     120
tcaaattatg tgtttttgg agagtcatgt cagtggtagt aatataattg ttgggacnat
                                                                     180
tagntttagc attggagtag gtttaggtta tgtacgtagn ctaggccata tgtgttggag
                                                                     240
                                                                     261
attganacta gtagggctag g
      <210> 704
      <211> 381
      <212> DNA
      <213> Homo sapien
     <220>
     <221> misc_feature
      <222> (1)...(381)
     <223> n = A,T,C or G
      <400> 704
ngtntgaatt ctattaaaga tacaaagagg agctggtacc atttcttctg aaactattac
                                                                      60
                                                                     120
aaacaactga aaaggtggaa tttctcccta attcatttta ggaggccagc attatactga
                                                                     180
taccaaaacc tggcagaggt acaataataa aaggaaactt caagtcagta tcactgatga
                                                                     240
acaccaatgt gaaaatcctc aataaaatac tggcaaactg aattcagcag cacatcaaaa
agctaatcca ccacaatcaa gtcagcttca tccctgcgat gcaagtctgg ttcaacatat
                                                                     300
gcaaatcaat aaatacaatt catcagataa acagagctaa agacaaaatt cacatgattt
                                                                     360
                                                                     381
tctcaataga tgcagaaaag g
     <210> 705
      <211> 477
      <212> DNA
      <213> Homo sapien
     <400> 705
ctgaaccctc gtggagccat tcatacaggt ccctaattaa ggaacaagtg attatgctac
                                                                     60 . . .
                                                                     120
ctttgcacgg ttagggtacc gcggccgtta aacatgtgtc actgggcagg cggtgcctct
aatactggtg atgctagagg tgatgttttt ggtaaacagg cggggtaaga tttgccgagt
                                                                     180 -
                                                                     240
tccttttact ttttttaacc tttccttatg agcatgcctg tgttgggttg acagtgaggg
taataatgac ttgttggtga ttgtagatat tgggctgtta attgtcagtt cagtgtttta
                                                                     300
                                                                     360
atctgacgca ggcttatgcg gaggagaatg ttttcatgtt acttatacta acattagttc
                                                                     420
ttctataggg tgatagattg gtccaattgg gtgtgaggag ttcagttata tgtttgggat
                                                                     477
tttttaggta gtgggtgttg agcttgaacg ctttcttaat tggtggctgc ttttagg
      <210> 706
     <211> 266
      <212> DNA
     <213> Homo sapien
     <220>
     <221> misc feature
     <222> (1)...(266)
      <223> n = A, T, C \text{ or } G
      <400> 706
60
                                                                     120
ggaggttagt tgtggcaata aaaatgatta aggatactan tataagagat caggntcgtc
                                                                     180
ctttagtgtt gtgtatggct atcatttgtt ttgaggntag tttgattagt cattgttggg
tggtaattag tcggttgttg atgagatatt tggaggtggg gatcaataga gggggaaata
                                                                     240
```

```
gaatgatcag tactgcggcg ggtagg
                                                                         266
       <210> 707
       <211> 358
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc feature
       <222> (1)...(358)
       <223> n = A, T, C \text{ or } G
       <400> 707
ccatcagaga aatgcaaatc aaaaccacaa tgagatacca tctcacacca gttagaatgg
                                                                          60
caatcattaa aaagtcagga aacaacaggt gctggagagg atgtggagaa ataggaacac
                                                                         120
ttttacaccg ntggtgggac tgtaaactag ttcaaccatt gtggaagtca gtgtggcgat
                                                                         180
tcctcaagga tctagaacta gaaataccat ttgacccagc cggccaatat tcaacattct
                                                                         240
taaaggaaag aattttcaac ccagaatttc atatccagcc aaactaagct tcgttagtga
                                                                         300
aggagaaata aaatacttta cagacaagca aatactgaga gattttgtca ccaccagg
                                                                         358
       <210> 708
       <211> 491
       <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(491)
      <223> n = A, T, C or G
      <400> 708
cctactatgg gngttaaatt ttttactctc tctacaaggt tttttcctag tgtccaaaga
                                                                         60
gctgttcctc tttggactaa cagttaaatt tacaagggga tttagagggt tctgtgggca
                                                                         120
aatttaaagt tgaactaaga ttctatcttg gacaaccagc tatcaccagg ctcggtaggt
                                                                        180
ttgtcgcctc tacctataaa tcttcccact attttgctac atagacgggt gtgctctttt
                                                                        240
agctgttctt aggtagctcg tctggtttcg ggggtcttag ctttggctct ccttgcaaag
                                                                        300
ttatttctag ttaattcatt atgcagaagg tataggggtt agtccttgct atattatgct
                                                                        360
tggttataat ttttcatctt tcccttgcgg tactatatct attgcgccag gtttcaattt
                                                                        420
ctatcgccta tactttattt gggtaaatgg tttggctaag gttgtctggt agtaagggng
                                                                        480
gagtgggttt g
                                                                        491
      <210> 709
      <211> 460
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(460)
      <223> n = A, T, C \text{ or } G
      <400> 709
nggttttttt tgtagagcaa ataatttatg caaaatatgt tacaaaatct gggatgctaa
                                                                         60
atagttgaca caagtactgt gtttgacatt tagtttcatt tgaattagta atagaatttg
                                                                        120
ctccttccaa catttacatc ttttttcttt ctgactttat atattttcaa taaaaatttg
                                                                        180
```

```
ctccacagtt tttaagntca ttcttcttga atccgntttt acatttgctg ngacaaacct
                                                                        240
gcataaaact agattttata gatataactt ctttggaaga gataaaaaatt caaaagtttg
                                                                        300
acattgcttt canttattct tttcttcatt gttttgattg gcccctgtta gattgatgta
                                                                        360
ttgccaatct acttttgatg gcatgaatnt aaaatgacaa cataaaaagc ncttctaqtg
                                                                        420
caacagtaat tgaaacttgc agttttccat taaaaaaaaa
                                                                        460
      <210> 710
      <211> 542
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(542)
      <223> n = A, T, C or G
      <400> 710
ctgttacagt gacaagagat aaaaagatag acctgcagaa aaaacaaact caaagaaatg
                                                                        60
                                                                        120
tgttcagatg taatgtaatt ggagtgaaaa actgtgggaa aagtggagtt cttcaggctc
ttcttggaag aaacttaatg aggcagaaga aaattcgtga agatcataga tcctactatg
                                                                        180
                                                                        240
cgattaacac tgtttatgta tatggacaag agaaatactt gttgttgcat gatatctcag
aatcggaatt tctaactgaa gctgaaatca tttgngatgt tgtatgcctg gtatataatg
                                                                        300
tcagcaatcc caaatccttt gaatactgtg ccaggatttt taagcaacac tttatggaca
                                                                        360
gcagaatacc ttgcttaatc gtagctgcaa agtcagacct gcatgaagtt aaacaagaat
                                                                        420
                                                                        480
acagtatttc acctactgat ttctgcagga aacacaaaat gcctccacca caagccttca
cttqcaatac tqctqatqcc cccaqtnaqq atatctttgt taaattgaca acaatggacc
                                                                        540.
                                                                        542
tg
      <210> 711
      <211> 394
      <212> DNA
      <213> Homo sapien
     <220>
      <221> misc_feature
      <222> (1)...(394)
      <223> n = A, T, C \text{ or } G
      <400> 711
caaacccact ccaccttact accagacaac cttagccaaa ccatttaccc aaataaagta
                                                                        60
                                                                       120
taggcgatag aaattgaaac ctggcgcaat agatatagta ccgcaaggga aagatgaaaa
attataacca agcataatat agcaaggact aacccctata ccttctgcat aatgaattaa
                                                                       180
ctanaaataa ctttqcaaqq aqaqccaaaq ctaaqacccc cgaaaccaga cgagctacct
                                                                       240
aagaacagct aaaagagcac acccgtctat gtagcaaaat agtgggaaga tttataggna
                                                                       300
gaqqcqacaa acctaccqaq cctggtgata gctggttgtc caagatagaa tcttagttca
                                                                       360
                                                                       394
actttaaatt tgcccacaga accctctaaa tccc
      <210> 712
      <211> 552
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(552)
```

```
\langle 223 \rangle n = A,T,C or G
       <400> 712
 gaggtctgta naatgccagg ctcaaatttg tctttataat ttaataccag aaatctttcc
                                                                         60
 cttgtgatgt ttctttcttt ctggattgcc tctatagcag gggatagcgg gggaggataa
                                                                         120
 ggcacatctt tgntgtactg agaaatttga ccacgcagga tgatgtggct gttctcattc
                                                                         180
 atctgcacag agaaaaataa tgataaaata tccctttcct atgtttactg attttatggc
                                                                         240
 tgccataatg gaagcctcct tgactattta atcctttctg tcaactaggt tcgattttt
                                                                         300
 ttttaattta cctgttagag gtatttaana attttaacta gctanaaata attacattcc
                                                                         360
 aaaggaacac caaggcaaat aaatggttgg taatcagcaa aagaattaca ttagttgttg
                                                                         420
ntgctactta ttagggggag aactgtttt ttttaaattt aaacaattta ataatctcaa
                                                                         480
ctgcaaataa ttttagatgc agcaaaggac tatgtagncg ttaatacctc atgttgatat
                                                                         540
 tttcataata tt
                                                                         552
      <210> 713
       <211> 518
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(518)
      <223> n = A, T, C \text{ or } G
      <400> 713
ccaaaaactg gaagcagctc actaaacaaa cagtggcata cccatagaac tgcatacttc
                                                                         60
tcagcagtat gaaagaatga gctacttata taagcatcat tgataaacct caaaaaaaaa
                                                                        120
atgccacatg aanaaaccca aagggganaa acataaaaac tttatatgtc agtcatataa
                                                                        180
aattctanaa aatgcaaact aatccatcnt aaaggaaagt aaatcaacag ttgtctggag
                                                                        240
gaccananag agcaggagga ganagattat taaaggggtt aaagtaaatt tgggagtgcc
                                                                        300
cttccntttt taaatnctat gaaaatgaaa gtaaaggcnc atgcatgttg taaactaata .
                                                                        360
gtaacaaaca naatgggttg gagtggggtg ttgtctgggg acatcattac aaaatgtaag
                                                                        420
ccagtttatn taaattttga aaagaccgtg gactctgatc tgactgatna atgttggaag
                                                                        480
agataagtgt gctgcaaatg ggggaattaa taaaacag
                                                                        518
      <210> 714
      <211> 281
      <212> DNA
      <213> Homo sapien
      <400> 714
ccaattgatt tgatggtaag ggagggatcg ttgacctcgt ctgttatgta aaggatgcgt
                                                                         60
agggatggga gggcgatgag gactaggatg atggcgggca ggatagttca gacggtttct
                                                                        120
atttcctgag cgtctgagat gttagtatta gttagttttg ttgtgagtgt taggaaaagg
                                                                        180
gcatacagga ctaggaagca gataaggaaa atgactatga gggcgtgatc atgaaaggtg
                                                                        240
ataagctctt ctatgatagg ggaagtagcg tcttgtagac c
                                                                        281
      <210> 715
      <211> 443
      <212> DNA
      <213> Homo sapien
      <400> 715
cttgaaatca gcaacacat tacaaatgag aaaatgaaaa tagaagagta tataaagaaa
                                                                        60
```

gggaaagagg attatgaaga gagtcatcag agagctgtgg ctgcagaggt atccgtactt

```
gaaaactgga aqqaqaqtga aqtgtataag ctacagatca tggagtcaca agcagaagcc
                                                                        180
                                                                        240
tttctgaaga agctggggct gattagccgt gatcctgcag catatcccga catggagtct
gatatacgtt catgggaatt gtttctttct aatgttacaa aagaaattga gaaagcaaag
                                                                        300
                                                                        360
tctcagtttg aagaacaaat taaggcaatt aaaaatggtt cccggctcag tgaactttct
aaagtgcaga tttctgagct ttcatttcct gcctgtaaca cggttcatcc cgagttactc
                                                                        420
                                                                        443
cctgagtctt caggccacga tgg
      <210> 716
      <211> 639
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(639)
      <223> n = A, T, C or G
      <400> 716
ccaaanaaaa tgaagtacag agtctgcata gtaagcttac agataccttg gtatcaaaac
                                                                         60
aacagttgga gcaaagacta atgcagttaa tggaatcaga gcagaaaagg gtgaacaaag
                                                                        120
                                                                        180
aagagtotot acaaatgoag gttoaggata ttttggagca gaatgaggot ttgaaagoto
aaattcagca gttccattcc cagatagcag cccagacctc cgcttcagtt ctagcagaag
                                                                        240
aattacataa agtgattgca gaaaaggata agcagataaa acagactgaa gattctttag
                                                                        300
caagtgaacg tgatcgttta acaagtaaag aagaggaact taaggatata cagaatatga
                                                                        360
                                                                        420
atttcttatt aaaagctgaa gtgcagaaat tacaggccct ggcaaatgag caggctgctg
                                                                        480
ctgcacatga attggagaag atgcaacaaa gtgtttatgt taaagatgat aaaataagat
                                                                        540
tqctqqaaqa qcaactacaa catqaaattt caaacnaaat qqaagaattt angattctaa
                                                                        600
atgaccaaaa canagcatta aaatcagaag ttcagaagct gcagactctt gtttctgcac
angcctaata aggatgntgn ggaacaaatg gaaaaattg
                                                                        639
      <210> 717
      <211> 473
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(473)
      \langle 223 \rangle n = A,T,C or G
      <400> 717
                                                                         60
nntgaggcta ctgctgtttt attacaacat tacctcttgt ttttataaag tgtaccaaga
tttaaattga taactttatt ttacttgaaa aaaaaaagtt tnttttatca ccagtgttac
                                                                        120
agttgtcttc tgtttctttt tgttttgntt tatttgnttt cctttttagc caaagagtga
                                                                        180
                                                                        240
acagaanatt ttcttatttt ggtggctatt cattttactt ttaaaagtga ttggtggatt
ttagactaat tatgggggaa tttgccacca aaataaaaaa tatgtaaagn gtagtgatta
                                                                        300
                                                                        360
cagagtggtt aaaatgtggg ttagtactta tttattccat taattgatta tttgactgtt
tataaaqaaa gttgctttat ttctttaaac atcttcaaaa gatgatcctt tcttgtcaca
                                                                        420
ttataqccaa aagaaqcaga qaacttcact qtctgcattt ggttcctggt tgg
                                                                        473
      <210> 718
      <211> 207
      <212> DNA
```

<213> Homo sapien

```
<400> 718
 ggtaaatgct agtataatat ttaccatctc acttctagga atactagtat atcgctcaca
                                                                          60
 cctcatatcc tccctactat gcctagaagg aataatacta tcactgttca ttatagctac
                                                                         120
 tctcataacc ctcaacaccc actccctctt agccaatatt gtgcctattg ccatactagt
                                                                         180
 ctttgccgcc tgcgaagcag cggtagg
                                                                         207
       <210> 719
       <211> 255
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(255)
       <223> n = A, T, C \text{ or } G
       <400> 719
cctatattac ggatcatttc tctactcaga aacctgaaac atcggcatta tcctcctgct
                                                                          60
tgcaactata gcaacagcct tcataggcta tgtcctcccg tgaggccaaa tatcattctg
                                                                         120
aggggccaca gtaattacaa acttactatc cgccatccca tacattggga cagacctagt
                                                                         180
tcaatgaatc tgaggaggct actcagtaga cagncccacc ctcacacgat tctttacctt
                                                                        240
tcacttcatc ttgcc
                                                                        255
      <210> 720
      <211> 455
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(455)
      <223> n = A, T, C or G
      <400> 720
ccaatgtcga aacctacaag atttccttaa aatctctaat agaggcatta cttgctttca
                                                                         60
attgacaaat gatgccctct gactagtaga tttctatgat ccttttttgt cattttatga
                                                                        120
atatcattga ttttataatt ggtgctattt gaanaaaaaa atgtacattt attcatagat
                                                                        180
agataagtat caggtctgac cccagtggaa aacaaagcca aacaaaactg aaccacaaaa
                                                                        240
aaaaaggctg gtgttcacca aaaccaaact tgttcattta gataatttga aaaagctcca
                                                                        300
tagaaaaggc gtgcagtact aagggaacaa tccatgtgat taatgnttnc attatgttca
                                                                        360
tgtaanaagc cccttatttt tagccataat tttgcatact gaaaatccaa taatcagaaa
                                                                        420
agtaattttg ccacattatt tatnaaaaat gttcc
                                                                        455
      <210> 721
      <211> 530
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(530)
      <223> n = A,T,C \text{ or } G
      <400> 721
```

ccagtgcttg ctgccgtggt ttagtgattg ggtgttagaa ataaaaactc aggtctattt

```
cttaccagtc agtaacaatt tttagagaat gtacttggta tataatatat ggacttcagg
                                                                        120
aactttattg gggngggggg ttaattttgc cttaccctgt tcactttcag atgattaggc
                                                                        180
ttttgcactt tagaatgaga aacttgtgac gttagtgtgt tcttactagc tttaatttgt
                                                                        240
atgtagcaat gaattgtgaa tottagtgca gtgggttttt ttaaaaaaact caaaaagctg
                                                                        300
ggaattaagt ggtttcagta ataatgctat accgaggtgc ttgcattgta tttcataatt
                                                                        360
ttgttacaaa ccaaaattat ttttaatgan aacggtcttg ggttcagagg tgtgatgcca
                                                                        420
gaatgtattt tegtaetgtt aggeeettgg aacagatace ggtgetttet tgaaagatga
                                                                        480
aagaaatgca atgggtgctc ttcatgcaag gttgcaaacc taccaagaat
                                                                        530
      <210> 722
      <211> 242
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(242)
      <223> n = A, T, C or G
      <400> 722
ccaaqqqtca tqatqqcaqq aqtaatcana qqtqntcttg tqttqtqata aqqqnqqaqa
                                                                         60
ggttaaagga gccacttatt agtaatgttg atagtagaat gatggctagg gtgacttcat
                                                                        120
atgagattgt ttgggctact gctcgcagtg cgccgatcag ggcgtagttt gagtttgatg
                                                                        180
ctcatcctga tnagaggatt gagtaaacgg ctaggctaga ggtggctaga ataaatagga
                                                                        240
                                                                        242
gg
      <210> 723
      <211> 472
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(472)
      <223> n = A, T, C \text{ or } G
      <400> 723
cctactatgq qtgttaaatt ttttactctc tctacaaggt tttttcctag tgtccaaaga
                                                                         60
gccgttcctc tttggactaa cagttaaatt tacaagggga tttagagggt tctgtgggca
                                                                        120
aatttaaagt tgaactaaga ttctatcttg gacaaccagc tatcaccagg ctcggtaggt
                                                                        180
ttgtcgcctc nacctataaa tcttcccact attttgctac atagacgggt gtgctctttt
                                                                        240
agetgttett aggtageteg tetggntteg ggggtettag etttggetet cettgeaaag
                                                                        300
ttatttctag ttaattcatt atqcaqaaqq tataqqqqtt aqtccttqct atattatgct
                                                                        360
tggttataat ttttcatctt tcccttgcgg tactatatct attgcgccag gtttcaattt
                                                                        420
ctatcgccta tactttattt gggtaaatgg tttggctaan gttgtctggt ag
                                                                        472
      <210> 724
      <211> 292
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(292)
      <223> n = A, T, C \text{ or } G
```

```
<400> 724
 nccaccactg cagccctaca tacagntgaa aaaaaattcc attctgttaa catttgtttt
                                                                          60
 ataagtttto acncaataca caaaaaacco ototgoactt ottgtaaaga acaaaaaaga
                                                                         120
 tacacaacag ttaagcgtaa agatcacagg caatagcatt caaacatgga tgtgggnaga
                                                                         180
 gaaaggagta cctggcatga gtacctgctt agttngactg aatccttgat ttttaatttg
                                                                         240
 gcttttcatg ggccgntcac aacaccaacg ctgngngagg tatggtagtc ag
                                                                         292
       <210> 725
       <211> 122
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(122)
       <223> n = A, T, C \text{ or } G
       <400> 725
 atagaaaggg catacccaaa atgttactga aaatntaata caaattccaa gattcaccaa
                                                                          60
 ngaagtaaca aaaacetgge etgeangngg neecetatee egtggeteea tggntgatgt
                                                                         120
· gg.
                                                                         122
       <210> 726
       <211> 477
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(477)
       <223> n = A,T,C or G
       <400> 726
 ctgaaccctc gtggagccat tcatacaggt ccctaattaa ggaacaagtg attatgctac
                                                                         60
 ctttgcacgg ttagggtacc gcggccgtta aacatgtgtc actgggcagg cggtgcctct .
                                                                        120
 aatactggtg atgctagagg tgatgttttt ggtaaacagg cggggtaaga tttgccgagt :
                                                                        180
 tccttttact ttttttaacc tttccttatg agcatgcctg tgttgggttg acagtgaggg
                                                                        240
 taataatgac ttgttggtga ttgtanatat tgggctgtta attgtcagtt cagtgtttta
                                                                        300
 atctgacgca ggcttatgcg gaggagaatg ttttcatgtt acttatacta acattaqttc
                                                                        360
 ttctataggg tgatagattg gtccaattgg gtgtgaggag ttcagttata tgtttgggat
                                                                        420
 tttttaggta gtgggtgttg agettgaacg etttettaat tggeggetge ttttagg
                                                                        477
       <210> 727
       <211> 416
       <212> DNA
       <213> Homo sapien
       <400> 727
 cctgtctttg aatggatgaa ataggttaat aaaaaacatc actgtttaaa aactaqaaca
                                                                         60
 ctgaaaaatt ctaggaaagc ttattttccc ttatattttt atggtacttt caacacttaa
                                                                        120
 taacactatt tcaattaagt tttctcctag agtttatagt atatcagtac attctttct
                                                                        180
 gtggatgcaa taatatagaa tettatteea aatettaetg geaggttete ttaaattett
                                                                        240
 caacggctgc catagtgatt aaccaaaatt agttatgatt tctgcctatc tgtgtgagaa
                                                                        300
 cttacagggg aaattgttct aaacctgagg aacatgaagt aactgtactg cacactccaa
                                                                        360
```

```
atgatgacag tcattttata tcaccttcaa ttacccaaca gcttttaata gtctgg
                                                                        416
      <210> 728
      <211> 416
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(416)
      <223> n = A, T, C \text{ or } G
      <400> 728
cctgtctttg aatggatgaa ataggttaat aaaaaacatc actgtttaaa aactagaaca
                                                                        60
ctqaaaaatt ctaggaaagc ttattttccc ttatattttt atggtacttt caacacttaa
                                                                       120
taacactatt tcaattaagt tttctcctag agtttatagt atatcagtac attcttttct
                                                                        180
qtqqatqcaa taatataqaa tcttattcca aatcttactg gcaggttctc ttaaattctt
                                                                       240
caacggctgc catagtgatt aaccaaaatt agttatgatt tctgcctatc tgtgtgagaa
                                                                        300
cttacagggg aaattgttct aaacctgagg aacatgaagt aactgtactg cacactccaa
                                                                       360
atqatqacaq tcattttata tcaccttcaa ttacccaaca gcttttaata ntctgg
                                                                       416
      <210> 729
      <211> 564
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(564)
      <223> n = A, T, C or G
      <400> 729
                                                                        60
ctgtgagtag aggagtcttc ccgagagtag cagttgttga tccaaatgat tgaagccttc
aggtaaggga ataactgctg caggaattct ttcttgaaga atttaagctg tttggtaaga
                                                                       120
                                                                       180
attotgtaac tacatacott tgaaacacta ttoacattoa aataaacgot tgttttotag
ccaggcacag gctcaattag tttttcaaac tctagccaag gcagtatttc atttgggaaa
                                                                       240
tcatqcaaca qaactqctca attcttaact tctcctqctq ttaacattta cacttagact
                                                                       300
                                                                       360
gccagcaaca gttaacttaa attttggtct caagggaaca aaaaaaaatt gcattcagaa
tttaatataq tattttaaaa ctaattttaq cctqtaagnc attatgagca atagtaactt
                                                                       420
ttatacctcc tcatcttgnc tgataatata ttctatatgc tgncaatctg attatatagt
                                                                       480
ctatatgcta gaagttgctg attttcattc tgccaccaaa aaaaactgtc ctttttttt
                                                                       540
tatgggggaa aaagggaatt taaa
                                                                       564
      <210> 730
      <211> 310
      <212> DNA
      <213> Homo sapien
      <400> 730
ccatttttat ttcttcttca gagaagtgtt tatttaggtc tgttgcccat tttacaatta
                                                                        60
qqccatatqt tttcttqctq ttqaqttqta tqtqtqtttq tataaatttt qcatattaac
                                                                       120
cccttatcac acgtatgttt tttaaaataa attttgctta ttaatctttt atcagatgta
                                                                       180
tggtttccaa atatattctt ccgatccatg gattctcttt tttgttatga ttgtttcttt
                                                                       240
gctcttcgga agctttttgt tttgttttgt tatttgtttt actttgatat agtcccattt
                                                                       300
attgtttttg
                                                                       310
```

```
<210> 731
      <211> 467
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(467)
      <223> n = A,T,C or G
      <400> 731
ngacaacctt agccaaacca tttacccaaa taaagtatag gcgatagaaa ttgaaacctg
                                                                        60
gcgcaataga tatagtaccg caagggaaag atgaaaaatt ataaccaagc ataataaagc
                                                                       120
aaggactaac ccctatacct tctgcataat gaattaacta gaaataactt tgcaaggaga
                                                                       180
gccaaagcta agacccccga aaccagacga gctacctaag aacagctaaa agagcacacc
                                                                       240
cgtctatgta gcaaaatagn gggaagattt ataggnagag gcgacaaacc taccgagcct
                                                                       300
ggtgatagct ggttgtccaa gatagaatct tagntcaact ttaaatttqc ccacaqaacc
                                                                       360
ctctaaatcc ccttgtaaat ttaactgnta gnccaaagag gaacagntct ttggacacta
                                                                       420 .
ggaaaaaacc ttgtagagag agtaaaaaat ttaacaccca tagtagg
                                                                       467
      <210> 732
      <211> 492
      <212> DNA
      <213> Homo sapien
      <220> '
      <221> misc_feature
      <222> (1)...(492)
      <223> n = A,T,C or G
      <400> 732
cctactatgg gtgttaaatt ttttactctc tctacaaggt tttttcctag tgtccaaaga
                                                                        60
gctgttcctc tttggactaa cagctaaatt tacaagggga tttagagggt tctgtgggca
                                                                       120 .
aatttaaagt tgaactaaga ttctatcttg gacaaccagc tatcaccagg ctcggtaggt
                                                                       180
ttgtcgcctc tacctataaa tcttcccact attttgctac atagacgggt gtgctctttt
                                                                       240
agetgttett aggtageteg tetggntteg ggggtettag etttggetet cettgeaaag
                                                                       300
ttatttctag ttaattcatt atgcagaagg tataggggtt agnccttgct atattatgct
                                                                       360
tggntataat ttttcatctt tcccttgcgg tactatatct attgcgccag gtttcaattt
                                                                       420
ctatcgccta tactttattt gggtaaatgg tttggctaag gttgtctggt agtgaggcgg
                                                                       480
agngggtttg gg
                                                                       492
      <210> 733
      <211> 562
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
     <222> (1)...(562)
      <223> n = A, T, C or G
      <400> 733
ntgaaatggc aatagcattc actgtcgtat tttgcagtgc tcaggaagtg ggacgttaac
                                                                        60
tttgaaggtg cttgtttgta ttagctctgc taggtttacc tctacaacgt agatttcagc
                                                                       120
```

```
180
agctatgctq actgacacta cattctagtt cttaagattt tttttccana tccccccttc
cccagctaga catacgtagc atactttcat cttattcagt ctttctgtaa cctgctgctg
                                                                       240
                                                                       300
cttttaqtcc tcctcacctc agatcggaat caatggagtg ggcccagagg atacatttta
attccagtaa tggtaggtag atttgtcctg ctttctaaaa catctcctca tttcatattt
                                                                       360
ccactccata ttgattccat aagggaaaat taatgggtgn ttcctccttt agggaggcaa
                                                                       420
tgcaaagagn gtggacatct tctaatcttg aggaacagtn gttgatttcc cttgaaggag
                                                                       480
cttacatatt qactqtnttt cacaataacc tgnttgcccc agntcaatcc ctcattttaa
                                                                       540
                                                                       562
tacttaatgt tggtnctggg ct
      <210> 734
      <211> 265
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(265)
      <223> n = A, T, C or G
      <400> 734
                                                                        60
ngqtccaqaa caagagaaat aactgcagaa aacacatatg gttggaaacc atgcgcttgt
gactttttct gtagcctatg ggagtggaca gagtgggtaa cccaagatgt ttttaagact
                                                                       120
                                                                       180
gactggacta agaatggcgt acttatagcc aactacttcc cccctaatgt gactgaaggg
attcataatg atcacaatta gcattacggt taagtatttt agggttgacg tctaagctca
                                                                       240
                                                                       265
cacttgaaag gtatttatct aatgg
      <210> 735
      <211> 216
      <212> DNA
      <213> Homo sapien
      <400> 735
atttaatacg tgctcactgc tcggcacgcg ctgaagctac agttaacaat cagtgagcac
                                                                        60
atattaaatg ataaaataat gctgatggta aacattcata acagcagagt aagattttgg
                                                                       120
caqttttgtg tctcggtaac ataactgtaa ccttagatga acacctatcc Cttcatgatc
                                                                       180
                                                                       216
tgactttaga ggcaaggagt ttgtaacatc taatgg
      <210> 736
      <211> 285
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(285)
      <223> n = A,T,C or G
      <400> 736
ctgaaaggca acntggagac tagttagtct agtcccctca tattataaat tggtatgctg
                                                                        60
aggccaggca gtaaattgct atggagctct ccaatttaag gccagtttga ctccaagggt
                                                                       120
agggetteta gtaaaatttt gtgattaaat tggaaactet aatttatttt tetatgngtt
                                                                       180
tttqqtacct aatcctcata aqcaaqccat atttcaaggc tgatcaatga aaacaccaaa
                                                                       240
                                                                       285
taccaaagct tcctttccct tccaaattta ctgacccttt gtcag
```

```
<211> 509
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(509)
      <223> n = A,T,C or G
      <400> 737
agangaagaa gangaagatt aagggaaaag tacatcggtc aagaagagct caacaaaaca
                                                                        60
aagcccatct ggaccagaaa tcccgacgat attactaatg aggagtacgg agaattctat
                                                                        120
aagagcttga ccaatgactg ggaagatcac ttggcagtga agcatttttc agttgaagga
                                                                        180
cagttggaat tcagagccct tctatttgtc ccacgacgtg ctccttttga tctgtttgaa
                                                                       240
aacagaaaga aaaagaacaa catcaaattg tatgtacgca gagttttcat catqqataac
                                                                        300
tgngaggagc taatccctga atatctgaac ttcattagag gggtggnaga ctcggaggat
                                                                       360
ctccctctaa acatatcccg tgagatgttg caacaaagca aaattttgaa agttatcang
                                                                       420
aagaatttgg gtcaaaaaat gcttanaact ctttactgaa ctggcggaag atnaagagaa
                                                                       480
ctncaagana ttctatgagc agntctctt
                                                                       509
      <210> 738
      <211> 97
      <212> DNA
      <213> Homo sapien
      <400> . 738
cagtgaattg aatacgactc ctatagggcg aattgggccc tctagatgca tgctcgagcg
                                                                        60
gccgccagtg tgatggatat ctgcagaatt cgccctt
                                                                        97
      <210> 739
      <211> 209
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(209)
      <223> n = A,T,C or G
      <400> 739
ccgncagtgt gatggatatc tgcagaattc gcccttagcg gcccgcccgg qcagqqtcct
                                                                        60
tatatatagt agcttagttt gaaaaaatgt gaaggacttt cgtaacggaa gtaattcaag
                                                                       120
atcaagagta attaccaact taatgttttt gcattggact ttgagttaag attattttt
                                                                       180
aaatcctgag gactagcatt aattgacgg
                                                                       209
      <210> 740
      <211> 164
      <212> DNA
      <213> Homo sapien
      <400> 740
ccaagctaat gggtgacact gtgaatgcaa ctctaatgca gcctggcgta aatggtccta
                                                                        60
tgggcactaa ctttcaagtt aacacaaaca gaggaggtgg tgtgtgggaa tctggtgcag
                                                                       120
caaactccca gagtacatca tggggaagtg gaaatggcgc aaat
                                                                       164
```

```
<210> 741
      <211> 514
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(514)
      <223> n = A, T, C \text{ or } G
      <400> 741
                                                                         60
ccagtcagaa ttgagatgtg ctgtgagtgc aaaatacact caaatctaag acttagtatg
gaagaaaaag aagataaggt gnttcattaa taatctttta tattgattac atgttgaaat
                                                                        120
gatattttta atatactggg ttacataaac tgttattaag attaattttg cttgtttctt
                                                                        180
ttttaatatg gctactagaa aattaaaaaat tatgttgtgg ttcacattat atttctgttg
                                                                        240
aacaatqtqq acataqataa tctacaqtca ttacattaqc cttagaattt aqcatcatac
                                                                        300
ttttaagcac tctggggtac taacttgaac tcccagaaac ccataagcac actctgcata
                                                                        360
taaattattg caaaattcat tcttatctct ctgaaagata tgcattttaa gggtaaaaaag
                                                                        420
aattcacaaa atattgantc cttaacaaat gtcaattagt atatggagag agctaaagga
                                                                        480
                                                                        514
cttcntgtag actggtncat tggggaaaaa caga
      <210> 742
      <211> 439
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (439)
      <223> n = A,T,C or G
      <400> 742
                                                                         60 -
qcaqqtccta tqcataqtta ataaqqqnta taatctactc aacatggaaa atgggagcct
atttgcaaac acacgagtaa ttaaagtacc aattctctct tagtttcttt ttttatagtt
                                                                        120
qqnttatttt qcaattataa atqntaaaca tccctagaga tgaaagttaa aatggctgat
                                                                        180
cacagatcag tagcaaaata caaattgaca attcaaaatt ataaataaaa ctctgttgag
                                                                        240
                                                                        300
gatgtttaac tttgagcctc caaatttaag agctaagctt ggaagaaaca aatttatagg
ttatatttcc ctcttaaatt aaaaaacaaa cttcctctgg cagtagnttg tgaattcctt
                                                                        360
                                                                        420
tcattqnaat qataccatqa ttacaggatc aaaaatgctt aacttacttg ccattctgct
                                                                        439
cacatcatca cagttgttt
      <210> 743
      <211> 275
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(275)
      <223> n = A, T, C or G
      <400> 743
cangacgcta cttcccctat catagaagag cttatcacct ttcatgatca cgccctcata
                                                                         60
qtcattttcc ttatctqctc cctaqtcctq tatqcccttt tcctaacact cacaacaaaa
                                                                        120
ctaactaata ctaacatete agaegeteag gaaatagaaa cegtetgaae tateetgeee
                                                                        180
```

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gccatcatcc tagtcctcat cgccctccca tccctacgca tcctttacat aacagacgag
                                                                         240
 gtcaacgatc cctcccttac catcaaatca attgg
                                                                         275
       <210> 744
       <211> 295
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(295)
       <223> n = A, T, C \text{ or } G
       <400> 744
ctgtnctttt aaaaaatctg gatgtttttt atttagtgat tgttcgacaa ttagctgctt
                                                                         60
caaaacataa tgtgcattgc ttatgaatgc cttcatatac taatacagat actctgataa
                                                                         120
tattacactc taataaggat aatgctgaat tttgaaagga cacaaaacat ctaatgccaa
                                                                        180
fatatacatg attagecaae atetttgeta teaagaceae tegtttttaa ataaagatge
                                                                        240
aagtgtcagt tgtagattat tgggatgaag ctaaatcccc agaatgcagc agcag
                                                                        295
      <210> 745
       <211> 477
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(477)
      <223> n = A, T, C or G
      <400> 745
cgcgttactg tacatattgc tagcaggaga caactggaaa tactaaacaa atactggaat
                                                                         60
tcacattaca gacagacgaa accaacatgg atgccacaca taacttcctt tgtagtttca
                                                                        120
cagagageet attigtggtt geteaggtgg ggteataeat tgettgeaga aatggeetga
                                                                        180
tcatagetet atgaaacaat gaatteggaa tgaaatetta ceatgacace tetetgtagg
                                                                        240
aaagaaatgt tgcttcacgt gtgctaagtt gagataataa tatttcacat atttatatac
                                                                        300
agagaatcac tctcaaattt aacccaagat aagcaatagg atttgggggt gacttgtaca
                                                                        360
catttctaac aacacttttc ttttttctag aggtcactct caaacactga tatatcacta
                                                                        420
tagtttgagt gtanggattc agtaatcaaa ggttgttatt gcaaaagagc caggcag
                                                                        477
      <210> 746
      <211> 524
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(524)
      <223> n = A, T, C or G
      <400> 746
ctgtgaaatt gggttgggag agccaaaata ctttacaact tcagaccgga gaaaaggcca
                                                                        60
gaggtgtgaa gttagactct atgatgaaac agagtcgtct tttgcgatga catgttggga
                                                                        120
taatgaatcc attctacttg cacagagctg gatgccacga gaaacagtaa tatttgcctc
                                                                        180
agatgtaaga ataaattttg acaaatttcg gaactgcatg acagcaactg taatctcaaa
                                                                        240
```

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aaccattatt acaactaatc caqatatacc agaagctaac attctgctga attttatacg
                                                                        300
                                                                        360
agaaaataaa gaaacaaatg ttctggatga tgaaattgac agttatttca aagaatccat
aaatttaagt acaatagttg atgtctacac agntgaacaa ttaaagggaa aagctttgaa
                                                                        420
gaatgaagga aaagctgatc cttcctatgg catcctttat gcctacattt ccacactcaa
                                                                        480
cattgatgat gaaactcaaa agtagttcga aatagatgtt ccag
                                                                        524
      <210> 747
      <211> 456
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(456)
      <223> n = A, T, C \text{ or } G
      <400> 747
cctcagttct tgattgtggt tgacggggcg tcaccatgaa ggagcccatt tagtataaag
                                                                         60
                                                                        120
cttccaacct tttctcttaa tcgtttcttt aatcttttaa accatcttca agtgcatagg
                                                                        180
qqaqtttccq atgccaqagg atgaaagcaa gtgctttctc caccctctcc tcccagagtg
aaaacaaatc cttttgctga tacttgtttc aaaagcatcc attgtaaagc ttctcagtga
                                                                        240
                                                                        300
cacaaaatac tgagaggtaa ctttttatca atcaaaccac ataccccaat ttaacacctt
tcagtgctct gaattcaact gacagactaa agggtgtttc ctgtaacagt ctgaaatatt
                                                                        360
aagtgttttt tttgttttgt ttttaaatct tatttcagaa aacttcctct nggggtagga
                                                                        420
                                                                        456
aagtacacat gaagcagcaa agtaacgaag aaaaac
      <210> 748
      <211> 474
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (474)
      <223> n = A,T,C or G
      <400> 748
ccanaccagg gaaccaaatg cagacagnga agttctctgc ttcttttggc tataatgnga
                                                                         60
                                                                        120
caaqaaaggg atcatctttt gaagatgttt aaagaaataa agcaactttc tttataaaca
gtcaaataat caattaatgg aataaataag tactaaccca cattttaacc actctgtaat
                                                                        180
                                                                        240
cactacactt tacatatttt ttatttnggn ggcaaantcc cccataatta gtctaaaatc
                                                                        300
caccaatcac ttttaaaagt aaaatgaata gccaccaaaa taagaaaatc ttctgttcac
tctttqqcta aaaaqqaaaa caaataaaac aaaacaaaaa gaaacagaag acaactgtaa
                                                                        360
cactqqtqat aaaaqaaact tttttttac aagtaaaata aagttatcaa tttaaatctt
                                                                        420
ggncacttta taaaaacaag aggtaatgtt gtaataaaac agcagtagcc tcag
                                                                        474
      <210> 749
      <211> 355
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(355)
      <223> n = A, T, C \text{ or } G
```

241

<400> 749 cctgggtnna gnggctgact gnaacctcca cttcctgttc tcaggcaatc ctcctgcctc 60 agcctcctta gtagctggga ctacaggagt gtgcaaccat gcccaactaa tttttgtatt 120 tttaatagag acagggtttc accatgttga tcaggttggt ctccaactcc tqacctcagg 180 tgatccacct gtcccagcct cccaaagtgc tgggattaca ggcatgagcc accacqcccq 240 gnccaggata aagtaaaaat ttgtaagcac acaaggccct ttgcaacctg gctcctggtt 300 actactttaa ncctcctgcc ctcccaaatg tnctcactgt ttttctanac atacc 355 <210> 750 <211> 493 <212> DNA <213> Homo sapien <220> <221> misc feature <222> (1) ... (493) <223> n = A,T,C or G <400> 750 ccatgctggt ctcgaactcc tgaactcagg tgatccaccc gcctcagtct cccaatagat 60 tacatatatt attaatgaat tgcttccttt aacaccctat tcattgaatt ttccaqtaaa 120 ccacaattac taattactcc tgaaatcaga aaagaggtta aaaagatttt ataacagtat 180 cctatgaaat ctactacttt caagtaatag tagttgaatt accaaaaccc qtcactcaaq 240 ccaatgacta caattaagat atgagtaaca tttcctagat aaataaagtc aattaattat 300 atttgcatct gggaaataga gaaagtacat ataagccatg attttgaagn caaaagagag 360 agantattig ccaaggaggg gtgagttata gtatgtaatt ataacataca gaagcttttt 420 gtatgctggt aactaatttt aatttcctac attnttatgg agatttctgc tattcttgtc 480 ctattttcca cct 493 <210> 751 <211> 364 <212> DNA <213> Homo sapien <220> <221> misc feature <222> (1)...(364) $\langle 223 \rangle$ n = A,T,C or G <400> 751 cgaggtctgg naaggtcacc aagtctgccc aganagctca gaaggctaaa tqaatattat 60 ccctaatacc tgccacccca ctcttaatca gtggtggaag aacggtctca gaactgtttg 120 tttcaattgg ccatttaagt ttagtagtaa aagactggtt aatgataaca atgcatcgta 180 aaaccttcag aaggaaagga gaatgttttg nggaccactt tggttttctt ttttgcgtgt 240 ggcagtttta agttattagt ttttaaaatc agtacttttt aatggaaaca acttgaccaa 300 aaatttgtca cagaattttg agacccatta aaaaagttaa atgagataaa aaaaaaaaan 360 cntg 364 . <210> 752 <211> 498 <212> DNA

<220>

<213> Homo sapien

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```
<221> misc feature
      <222> (1)...(498)
      <223> n = A, T, C or G
      <400> 752
ctqqattatq qqttqqnatt qqtcatatqt tagactccat acaggcatag ctatgatgca
                                                                         60
gtgaatccct tagaagttac aattctcaaa ttacatactt cctcagatgt aacattagaa
                                                                        120
ctcaatattt ctaacaataa cataccagaa aaggctggac tggcactcat ctgctgacta
                                                                        180
acttgtagcc tcagtaatat gacatacttg cctttaacaa attatctcaa attaactaac
                                                                        240
agaccttcag aaaatggaga ttctttttga tggggacata atcaaattta agtctgagaa
                                                                        300
                                                                        360
atatqcttaa caqttqqaac tcaaattaaa tqtactqatt ttaaagttta gacattaaca
agtgatanat tagcctcaaa aaaagacaat ttggnaaggn ttaggtcttt taatttggtg
                                                                        420
cttqntcaca acttgactgg tgcttctttc cttgctgctt cacatcaagc atggggccaa
                                                                        480
                                                                        498
ttctattttc agtaaatg
      <210> 753
      <211> 467
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(467)
      <223> n = A,T,C or G
      <400> 753
                                                                         60
nacaacctta qccanaacca tttacccaaa taaagggata ggcgatagaa attgaaacct
                                                                        120
ggcgcaatag atatagnacc gcaagggaaa gatgaaaaat tataaccaag cataatatag
caaqqactaa cccctatacc ttctqcataa tgaattaact agaaataact ttgcaaggag
                                                                        180
agccaaagct aagaccccg aaaccagacg agctatctaa gaacagctaa aagagcacac
                                                                        240
                                                                        300
ccgtctatgt agcaaaatag tgggaagatt tataggtaga ggcgacaaac ctaccgagcc
tggtgatagc tggntgncca agatagaatc ttagntcaac tttaaatttg cccacagaac
                                                                        360
                                                                        420
cctctaaatc cccttqtaaa tttaactqtt aqtccaaaqa ggaacagctc ttggacacna
ggaaaaaacc ttgcagagag agtaaaaaat ttaacaccca tagtagg
                                                                        467
      <210> 754
      <211> 196
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(196)
      \langle 223 \rangle n = A,T,C or G
      <400> 754
                                                                         60
gtcatgttca agtgttntaa tctgacgcag gcttatgcgg aggagaatgt tttcatgtta
cttatactaa cattagttct tctatagggt gatagattgg tccaattggg tgtgaggagt
                                                                        120
                                                                        180
tcagttatat gtttgggatt ttttaggcag tgggtgttga gcttgaacgc tttcttaatt
                                                                        196
ggtggctgct tttagg
      <210> 755
      <211> 381
      <212> DNA
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<213> Homo sapien

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<400> 755
ctggaaagga ttctgtacat ataagacatc aaatattgag ggatactgga acttttaaat
                                                                        60
taatgggcaa agaaagtcaa caaaggaagt tcatatgaaa tcaaactagt aatatgatta
                                                                        120
caaaaaaaaa gtttaaaatt tttcttggcc ccagtcttat catttctgag ccaaatacaa
                                                                        180
ttctatcgaa atcacctgaa actgaaatca ccattctagg ctggttttcc cataaagatg
                                                                        240
gactgctcca aaaagaggaa tcaagaaaga atttggctca cagtgaatta ttcactttgt
                                                                       300
cttagttaac taaaaataaa atctgactgt taactacaga aatcatttca aattctgtgg
                                                                       360
tgataataaa gtaatgaccg c
                                                                       381
      <210> 756
      <211> 341
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(341)
      <223> n = A.T.C or G
      <400> 756
ggntataaac ctattattta ttgcagaact aataaaaaat ccaaagcctt gtatttgtac
                                                                        60
atctttatta tctctaaagc actttcctca acctaatttc agtttttaca attggtactc
                                                                       120
aagaaaatag agacagaaat catttgattt tgcccagaaa ccatctgctt atatttataa
                                                                       180
ggccacctaa tttgaaatca catatagacc aggcgcggtg gctcacgcct gtaattccaa
                                                                       240
cactttggaa ggccaaggca ggtggatcac aaggtcaaga gattgagacc atcttggcca
                                                                       300
acatggcgaa accccgtctc taccaaaaat acaaaaatca g
                                                                       341
      <210> 757
      <211> 479
      <212> DNA
    < <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(479)
      <223> n = A, T, C \text{ or } G
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ttcacattac agacagacga aaccaacatg gatgccacac ataacttcct ttgtagtttc
                                                                       120
acagagagcc tatttgtggt tgctcaggtg gggtcataca ttgcttgcag aaatggcctg
                                                                       180
atcatagete tatgaaacaa tgaattegga atgaaatett accatgacae etetetgtag
                                                                       240
gaaagaaatg ttgcttcacg tgtgctaagt tgagataata atatttcaca tatttatata
                                                                       300
cagagaatca ctctcaaatt taacccaaga taaqcaataq gatttqqqqq tqacttqtnc
                                                                       360
acatttctaa caacactttt ctttttcta gaggtcactc tcaaacactg atatatcact
                                                                       420
atagnttgag ngtagggatt caagtaatca aaggttgtta ttgcaaaaqa qccaqqcaq
                                                                       479
      <210> 758
      <211> 267
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
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<213> Homo sapien

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                                                                         60
 atgatttaca agatagaaca ctttaaacca ggtcagtcct atcttttgt agctgaaggc
                                                                        120
 tatcagtcat aacacaattt cgcgtacacc tctgctcatt atggaattac acttaaaacg
                                                                        180
 aatctcaaga gggtgaccat tgttgtttca gataccatcc ctaaggagag tggttaacag
                                                                        240
 gaagattgcc agtgttactg atggaaagaa gtgtttgttt gtttttttc ttgtcaaaga
                                                                        300
 cttacaccat agttttaaat taaactgtca ggcattttct cagacaggtt ttccttttca
                                                                        360
 atgcagtaat gaagaactaa gataaaaatc atgacttttg actgccactc aacattatta
                                                                        420
 catgcacc
                                                                        428
       <210> 762
       <211> 574
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
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      <223> n = A, T, C or G
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                                                                         60
gttcgaagtg aaaacctggg ctctttacca gtgttgagtg agaagattta tttctctttc
                                                                        120
ctctgaattt accacatgta acatcacaga gacatgtaga gttcctttag gatttgcgat
                                                                        180
ttgaaccagn ccagtctgat tttcaggtga attctgtgaa gagcttgatg ggggaagtct .
                                                                        240
gaagacagaa ggaattaggg aaaagggtga tacttacaga gtaaaggaaa taaatgaaaa
                                                                        300
gataatggta tttttggtag ccacagggaa atagcaggag gggactggag atcacacac
                                                                       360
cgcacacgca cacacacaaa cacacacaca cgctaaaact caaactaaaa acctcccaaa
                                                                       420
ggagctgctt tgtttgcaga cttcaattng aagtagatac taagggcaag aatagaccag
                                                                       480
ttaaaattca cctgaaaatc tcttcccann cttcaaatgt gctaaaatat cactgtcagc
                                                                       540
ttagcatctc tncatgtatg tatatataga tgta
                                                                       574
      <210> 763
      <211> 465
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(465)
      <223> n = A,T,C \text{ or } G
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                                                                        60
agetgtteet etttggaeta acagttaaat ttacaagggg atttagaggg ttetgnggge
                                                                       120
aaatttaaag ttgaactaag attctatctt ggacaaccag ctatcaccag gctcggtagg
                                                                       180
tttgtcgcct ctacctataa atcttcccac tattttgcta catagacggg tgtgctcttt
                                                                       240
tagctgttct taggtagctc gtctggtttc gggggtctta gctttggctc tccttgcaaa
                                                                       300
gttatttcta gttaattcat tatgcagaag gtataggggt tagtccttgc tatattatgc
                                                                       360
ttggatataa tttttcatct ttcccttgcg gtactatatc tattgcgcca ngtttcaatt
                                                                       420
tctatcgcct atactttatt tgggtaaatg gtttggctaa ggttg
                                                                       465
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      <211> 151
      <212> DNA
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aaaacattaa gttggtaatt actcttgatc ttgaattact tccgttacga aagtccttca
                                                                        120
catttttcaa actaagctac tatatttaag g
                                                                        151
      <210> 765
      <211> 251
      <212> DNA
      <213> Homo sapien
      <400> 765
                                                                        60
gaagagetta teacetttea tgateaegee eteatagtea tttteettat etgetteeta
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gtcctgtatg cccttttcct aacactcaca acaaaactaa ctaatactaa catctcagac
gctcaggaaa tagtaaccgt ctgaactatc ctgcccgcca tcatcctagt cctcatcgcc
                                                                        180
ctcccatccc tacgcatcct ttacataaca gacgaggtca acgatccctc ccttaccatc
                                                                        240
                                                                        251
aaatcaattg g
      <210> 766
      <211> 375
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      <213> Homo sapien
      <220>
      <221> misc_feature
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                                                                        60
                                                                        120
cataaaatct ttgggaaggg acaactgtaa aggaagttca tagtcgtcaa tatgaaggat
tttaatttct ggctttccta tcttcttctt caggatagct tccttcagca tagaattgtt
                                                                        180
                                                                        240
ttccaatata aaatattttg ctgggttgtc cgtactatgt aggctgacca ctgggaccct
tggaccttca cagaataata agaaatgttg attcatggga ctaaaactgg catcaaaata
                                                                        300.
tgtacattgt tctttcatga aattacatga aatgcattgg cgattcaata atccttcagt
                                                                        360
                                                                        375
agaagcactg tacag
      <210> 767
      <211> 485
      <212> DNA
      <213> Homo sapien
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      <221> misc_feature
      <222> (1)...(485)
      <223> n = A,T,C or G
      <400> 767
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                                                                        60
                                                                        120
tgctaccttn gcacggttag ggtaccgcgg cccgttaaac atgtgtcact gggcaggcgg
                                                                        180
tgcctctaat actggtgatg ctagaggtga tgtttttggn aaacaggcgg ggtaagattt
gccgagttcc ttttactttt tttaaccttt ccttatgagc atgcctgtgt tgggttgaca
                                                                        240
gtgagggtaa taatgacttg ttggtgattg tagatattgg gctgttaatt gtcagttcag
                                                                       300
                                                                       360
tgttttaatc tgacgcaggc ttatgcggag gagaatgttt tcatgttact tatactaaca
                                                                       420
ttagttcttc tatagggtga tagatnggtc caattgggtg tgaggagntc acttatatgt
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ttgggatttt ttaggtaagn gggtgttgag cttgaacgct ttcttaattg ggggctgctt
                                                                          480
 ttang
                                                                          485
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       <211> 379
       <212> DNA
       <213> Homo sapien
      <220>
      <221> misc_feature
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      \langle 223 \rangle n = A,T,C or G
      <400> 768
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                                                                          60
acaactgaaa aggtggaatt tctccctaat tcattttagg aggccagcat tatactgata
                                                                         120
ccaaaacctg gcagaggtac aataataaaa ggaaacttca agtcagtatc actgatgaac
                                                                         180
accaatgtga aaatcctcaa taaaatactg gcaaactgaa ttcagcagca catcaaaaag
                                                                         240
ctaatccacc acaatcaagt cagcttcatc cctgcgatgc aagtctggtt caacatatgc
                                                                         300
aaatcaataa atacaattca tcagataaac agagctaaag acaaaattca catgattttc
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tcaatagatg cagaaaagg
                                                                         379
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      <211> 518
      <212> DNA ·
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(518)
      <223> n = A, T, C \text{ or } G
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                                                                          60
atatgggtag aatatagtca atatgaatgg aatagacaat gctttgaaaa tcactggagg
                                                                         120
gaggetttat tgtttgtgaa aacatgttgt catcaetttt tgetttaage eettggtggt
                                                                         180
gaaataactc aaaccattct tccttatgct gaagatcgag aaccccaagt atcacatcta
                                                                         240
ccatcccact catcaatgtg attggtcagt ctttgctgag gncctgcata gccagtttta
                                                                         300
aagttagagt tettgeatat acatatgaaa aggeatgtta ettgtgettt caaagagett
                                                                         360
tttgcttggt gtaaaaagaa aactcaaatt acagtgtgat gtggaatata atggtggtag
                                                                         420
tttcatcgag atgatgggaa agaattgata agataaagcn gaaagatgag cagaattttc
                                                                         480
agattgggtn tggaaagagc acttaagaaa gagggtgg
                                                                         518
      <210> 770
      <211> 378
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(378)
      \langle 223 \rangle n = A,T,C or G
      <400> 770
tatgggtcct gagtgtggaa tataagataa caagacaatt cccttgcttt caagggaaat
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cacactttat aaaactttga attcttgaaa agaataagag ttaagaagaa aaagactatg aaatggcagg aatagtctca atctactcat gatattgcaa cttgctctct ctctttgcca ctgaattggc aagaaaaatg gctggagggc cttcttcctt ctttctcc	agaaaggaag tggggaaaaa ccccaccctt	tgntgacccc tgtatgttgc tgncatgctc	atttgcattt atatttttga tgtttttggg	120 180 240 300 360 378
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<210> 772 <211> 384 <212> DNA <213> Homo sapien				
<220> <221> misc_feature <222> (1)(384) <223> n = A,T,C or G				
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ttgtcgcctc tacctataaa tcttcccact agctgttctt aggtagctcg tctggtttcg ttatttctag ttaattcatt atgcagaagg tggttataat ttttcatctt tccc	ggggtcttag	ctttggctct	ccttgcaaag	240 300 360 384
<210> 773 <211> 182 <212> DNA <213> Homo sapien				·
<400> 773 cccttttcct aacactcaca acaaaactaa atagaaaccg tctgaactat cctgcccgcc ctacgcatcc tttacataac agacgaggtc gg	atcatcctag	tcctcatcgc	cctcccatcc	60 120 180 182
<210> 774 <211> 191 <212> DNA <213> Homo sapien				
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<213> Homo sapien

aggaggttag ttgtgg cctttagtgt tgtgta gtggtaatta g				_	120 180 191
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<400> 776					
ctgaccccct agaacc ggtctgttct ctccca aaaaaaaaaa aaaaaa	ttac acataggttt				60 120 144
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                                                                        120
atttcccaac agagatactt ctggtcttac tgcacagtct tttaagagaa atacttccat
                                                                        180
tatgccacat tgtccttgat ccgtaagtga tgtgttaagg tgcttcaaag gaactctgac
                                                                        240
ctctgaagta cttgagctac tttagtatgt ccagcctatt gctttttgtt ttagngngtc
                                                                        300
accataaata tcaggggcat aaaaggctat ctattcttaa ttcaaggata aaacagaaga
                                                                        360
                                                                        393
agcttgtggn ataaaacaat agtcaagatc cag
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      <211> 277
      <212> DNA
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      <220>
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gtagggatgg gagggcgatg aggactagga tgatggcggg caggatagtt cagacggttt
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ctatttcctg agcgtctgag atgttagtat tagttagttt tgttgtgagt gttaggaaaa
                                                                        180
gggcatacag gactaggaag cagataagga aaatgactat gagggcgtga tcatgaaagg
                                                                        240
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tgataagctc ttctatgata ggggaagtag cgtcttg
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      <221> misc feature
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attgtctaac tttttatttt tggnctggct gttgtggtgt gcaaaactcc gtacattgct
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attttqccac actgcaacac cttacagatg tggaagatgt gaaatttgtc atcaattatg
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actaccctaa ctcctcagag gattatattc atcgaattgg aagaactgct cgcagtacca
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aaacaqqcac aqcatacact ttctttacac ctaataacat aaagcagggg agcgacctta
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      <210> 781
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      <212> DNA
      <213> Homo sapien
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       <221> misc feature
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       <223> n = A, T, C \text{ or } G
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                                                                         120
taccaaagtg tgcaacctac agaccctcag gtactgccct gtgacttctc tgtatgacat
                                                                         180
cacaaggctg ccaagtgcct gtttttctag aactaggagt tggtgaggtt tggctantgc
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gacag
                                                                         305
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      <221> misc_feature
      <222> (1)...(497)
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                                                                        120
aacctggatg gttttcaatg gcatggttag tcaaattcat ggttttaaac ttagaagcag
                                                                        180 -
ctttcggggg agagggtagg ttggagcatt tattacatat tttactgttt aatgtcttaa
                                                                        240
ccgtgggcct tttaatttgt aaacactgaa atgattgttg ggctgtggaa aacatttacc
                                                                        300
tatttacctt ggaagtttta aaagacagtc cactttttag catgtgtgtt gcgtccagcc
                                                                        360
tgtggtcgtc ttaactaata aatgngattt ttctctcaaa aaaaaaacct ccccgggcgg
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                                                                        497
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      <211> 364
      <212> PRT
      <213> Homo sapien
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Ser Ser Gln Ile Ala Ala Ala Ser Thr Gln Pro Glu Asp Asp Ile
Asn Thr Gln Arg Lys Lys Ser Gln Glu Lys Met Arg Glu Val Thr Asp
                            40
Ser Pro Gly Arg Pro Arg Glu Leu Thr Ile Pro Gln Thr Ser Ser His
                        55
Gly Ala Asn Arg Phe Val Pro Lys Ser Lys Ala Leu Glu Ala Val Lys
                    70
                                         75
Leu Ala Ile Glu Ala Gly Phe His His Ile Asp Ser Ala His Val Tyr
                                     90
Asn Asn Glu Glu Gln Val Gly Leu Ala Ile Arg Ser Lys Ile Ala Asp
                                 105
Gly Ser Val Lys Arg Glu Asp Ile Phe Tyr Thr Ser Lys Leu Trp Ser
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Asn	Ser 130	His	Arg	Pro	Glu	Leu 135	Val	Arg	Pro	Ala	Leu 140	Glu	Arg	Ser	Leu
Lys 145	Asn	Leu	Gln	Leu	Asp 150	Tyr	Val	Asp	Leu	Tyr 155	Leu	Ile	His	Phe	Pro 160
Val	Ser	Val	Lys	Pro 165	Gly	Glu	Glu	Val	Ile 170	Pro	Lys	Asp	Glu	Asn 175	Gly
Lys	Ile	Leu	Phe 180	Asp	Thr	Val	Asp	Leu 185	Cys	Ala	Thr	Trp	Glu 190	Ala	Mèt
Glu	Lys	Cys 195	Lys	Asp	Ala	Gly	Leu 200	Ala	Lys	Ser	Ile	Gly 205	Val	Ser	Asn
Phe	Asn 210	His	Arg	Leu	Leu	Glu 215	Met	Ile	Leu	Asn	Lys 220	Pro	Gly	Leu	Lys
Tyr 225	Lys	Pro	Val	Cys	Asn 230	Gln	Val	Glu	Cys	His 235	Pro	Tyr	Phe	Asn	Gln 240
Arg	Lys	Leu	Leu	Asp 245	Phe	Cys	Lys	Ser	Lys 250	Asp	Ile	Val	Leu	Val 255	Ala
Tyr	Ser	Ala	Leu 260	Gly	Ser	His	Arg	Glu 265	Glu	Pro	Trp	Val	Asp 270	Pro	Asn
Ser	Pro	Val 275	Leu	Leu	Glu	Asp	Pro 280	Val	Leu	Cys	Ala	Leu 285	Ala	Lys	Lys
	290	_				Leu 295					300				
Gly 305	Val	Val	Val	Leu	Ala 310	Lys	Ser	Tyr	Asn	Glu 315	Gln	Arg	Ile	Arg	Gln 320
				325		Phe			330					335	
Ile	Asp	Gly	Leu 340	Asn	Arg	Asn	Val	Arg 345	Tyr	Leu	Thr	Leu	Asp 350	Ile	Phe
Ala	Gly	Pro 355	Pro	Asn	Tyr	Pro	Phe 360	Ser	Asp	Glu	Tyr				
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			6353	3											
		212>													
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Ser Pro Leu Leu Arg His Gly Gly His Thr Gln Thr Gln Asn His Thr

25

15

5

260

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40

45

261

Gly Ser Val Lys Arg Glu Asp Ile Phe Tyr Thr Ser Lys Leu Trp Ser

Thr Phe His Arg Pro Glu Leu Val Arg Pro Ala Leu Glu Asn Ser Leu 65 70 75 80

Lys Lys Ala Gln Leu Asp Tyr Val Asp Leu Tyr Leu Ile His Ser Pro 85 90 95

Met Ser Leu Lys Pro Gly Glu Glu Leu Ser Pro Thr Asp Glu Asn Gly
100 105 110

Lys Val Ile Phe Asp Ile Val Asp Leu Cys Thr Thr Trp Glu Ala Met
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<211> 2435

<212> DNA

<213> Homo sapiens

<400> 796

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<213> Homo sapiens

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Ser Pro Arg Cys Thr Thr Cys Arg 115 120

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263

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<211> 2477

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<213> Homo sapien

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<211> 1619

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<400> 803

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Phe Cys Ser Lys Thr Lys Ala Leu Ala Ala Ile Pro Pro Pro Val Pro 65 70 75 80

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Gly Ile Thr Ala Leu Leu Asn Val Ser Ser Asp Cys Pro Asn His Phe 130 135 140

Glu Gly His Tyr Gln Tyr Lys Cys Ile Pro Val Glu Asp Asn His Lys 145 150 155 160

Ala Asp Ile Ser Ser Trp Phe Met Glu Ala Ile Glu Tyr Ile Asp Ala 165 170 175

Val Lys Asp Cys Arg Gly Arg Val Leu Val His Cys Gln Ala Gly Ile 180 185 190

Ser Arg Ser Ala Thr Ile Cys Leu Ala Tyr Leu Met Met Lys Lys Arg 195 200 205

Ile Ser Pro Asn Phe Ser Phe Met Gly Gln Leu Leu Gln Phe Glu Ser 225 230 235 240

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280

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Ser His Gly Thr Leu Gly Leu Pro Ser Gly Gly Lys Cys Leu Leu Leu 35 40 45

Asp Cys Arg Pro Phe Leu Ala His Ser Ala Gly Tyr Ile Leu Gly Ser 50 55 60

Val Asn Val Arg Cys Asn Thr Ile Val Arg Arg Arg Ala Lys Gly Ser 65 70 75 80

Val Ser Leu Glu Gln Ile Leu Pro Ala Glu Glu Glu Val Arg Ala Arg 85 90 95

Leu Arg Ser Gly Leu Tyr Ser Ala Val Ile Val Tyr Asp Glu Arg Ser 100 105 110

Pro Arg Ala Glu Ser Leu Arg Glu Asp Ser Thr Val Ser Leu Val Val 115 120 125

Gln Ala Leu Arg Arg Asn Ala Glu Arg Thr Asp Ile Cys Leu Leu Lys 130 135 140

Gly Gly Tyr Glu Arg Phe Ser Ser Glu Tyr Pro Glu Phe Cys Ser Lys 145 150 155 160

Thr Lys Ala Leu Ala Ala Ile Pro Pro Pro Val Pro Pro Ser Ala Thr 165 170 175

Glu Pro Leu Asp Leu Gly Cys Ser Ser Cys Gly Thr Pro Leu His Asp 180 185 190

Gln Gly Gly Pro Val Glu Ile Leu Pro Phe Leu Tyr Leu Gly Ser Ala 195 200 205

Tyr His Ala Ala Arg Arg Asp Met Leu Asp Ala Leu Gly Ile Thr Ala 210 215 220

Leu Leu Asn Val Ser Ser Asp Cys Pro Asn His Phe Glu Gly His Tyr 225 230 235 240

Gln Tyr Lys Cys Ile Pro Val Glu Asp Asn His Lys Ala Asp Ile Ser 245 250 255

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